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THE  
INCIDENTAL  
EFFECTS OF DRUGS

A  
PHARMACOLOGICAL AND CLINICAL HAND-BOOK

BY  
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## TRANSLATOR'S PREFACE.

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A RECOGNITION of the importance of a knowledge of the incidental, accidental, or unexpected effects (*Nebenwirkungen*) of drugs upon the various organs and systems of the body, has led the translator of this manual to believe that it will prove of interest and advantage to a larger number of readers than it can obtain in its original form alone. The literature of the subject of which it treats, as far, at least, as he is familiar with it, is comparatively meagre, the only systematic work upon it being one confined to the study of a single organ, viz., a portion of the interesting book of Dr. H. G. Piffard, upon the "*Materia Medica and Therapeutics of the Skin*."

In view of the active interest which is at present taken in the study of *materia medica* and therapeutics, especially in this country, it is to be hoped that others may be stimulated to study and record with more care than in the past the peculiar actions of drugs upon individual organs.

W. T. A.

## PREFACE.

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THE science of *materia medica*, as an essential connecting link between purely experimental investigation and empiricism, receives contributions both from the laboratory and from observation at the bedside. The facts obtained from these sources present in their totality the picture of the typical mode of action of individual drugs.

But in the therapeutic employment of certain drugs, deviations sometimes occur from this typical and, as one may say, normal action, whose recognition and correct interpretation are not always easy. A knowledge of them is, however, of great importance to the physician, since they may, in a given case, shed light upon the cause of the unexpected phenomena which show themselves, and also furnish indications to guide him in his practical interference.

The individual facts bearing upon this subject, the phenomena of abnormal drug-action, are widely scattered through medical literature, and are either not at all mentioned, or are only superficially treated of in text-books on *materia medica* and therapeutics. For this reason I have for a long time occupied myself in collecting and annotating them, and in making additions to their number from my own experience. The result is contained in this work, which will, I hope, not only satisfy practical requirements, but also stimulate to further observations in this direction.

L. LEWIN.

BERLIN, January, 1881.

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# THE INCIDENTAL EFFECTS OF DRUGS.

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## INTRODUCTION.

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### § I.

DRUGS act locally in the animal economy, *i. e.*, they influence exclusively, or in a particular manner, according to their chemical or physical properties, certain classes of cells or cellular structures. "Certain substances have affinities for certain parts of the body" is an axiom first enunciated by Virchow,<sup>1</sup> upon which it follows as a natural consequence, that certain drugs, in addition to their curative effects, may, by either a direct or reflex action, produce symptoms affecting homologous or heterologous cell-groups which, for therapeutic purposes, should not be acted upon. After the administration of opiates, for instance, not only is an influence exerted upon the central nervous system, but also upon peripheral nerve-centres and nerves, so that, in addition to a more or less pronounced hypnotic effect, there occurs a temporary paralysis of the nerves which regulate the movements of the intestines, and in consequence of this, a stagnation of the intestinal contents. When tartar emetic is taken, vomiting occurs in consequence of irritation of the gastric mucous membrane, and at the same time, the activity of

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<sup>1</sup> Virchow: *Specificer und Specifisches*, Archiv f. path. Anatomie, Bd. vi., p. 24.

the heart is lessened by the direct action of the drug upon its substance. The inhalation of chloroform produces an effect upon the nerve-centres, particularly the cerebrum, and, by a reflex action from the respiratory mucous membrane, the action of the heart is also interfered with. While, therefore, homogeneous elements of a nervous nature, in different regions of the body, are affected by opium and chloroform, the antimony in tartar emetic exerts its influence upon heterogeneous tissues, viz., mucous membranes and muscles. In an analogous manner, substances which possess the inherent power of influencing a still greater number of cell-forms, may produce a whole chain of pathological symptoms. Such effects as these are, however, regarded as physiological, because while inseparable from one another, they belong in their totality to the action of the drug. The individual symptoms are only separated from each other when, in accordance with the therapeutic indication for the drug, it becomes desirable to distinguish between primary and incidental action.

## § 2.

Although, in this manner, nearly all active drugs exert the influences peculiar to themselves upon certain groups of cells, *e. g.*, a diseased organ, and thus bring about curative results, it not infrequently happens that in the cases of certain persons, the desired local effect is not produced, the drug proving itself "inactive." Thus, chloroform may fail to produce anæsthesia, quinine to reduce a swollen spleen, and cathartics, even those belonging to the class of drastics, to cause an evacuation.

If the drugs used be of good quality (which in this case is taken for granted), the cause of this anomalous result can lie only in the person taking the remedy. His organization, or the structure of the healthy or diseased parts upon which it is desired to act, must be different from that



of the same parts in other persons. The same postulate must be advanced for such individuals as possess an organization exceptional as regards its capacity for resisting disease, in consequence of which they are never attacked by certain contagious maladies, *e. g.*, exanthematic typhus. In the latter, as in the former cases, the immunity may be due, not to gross anomalies of structure, which will be discussed later at greater length, but to physiological differences in tissues or organs.

It will be readily understood that, if certain organs of an individual fail to respond to the action of certain drugs which ordinarily produce well-known functional effects, therapeutical experiments with these drugs may lead to erroneous conclusions, when made upon such persons. This fact may perhaps explain the often diametrically opposed results which follow the use of a given drug in different persons.

### § 3.

Of far greater importance to the physician than the non-occurrence of a normal drug effect, are the not infrequently observed *incidental effects of remedies*, which either take the place of the normal action, or appear simultaneously with it. The administration of quinine, for instance, is not uncommonly followed by the appearance of a polymorphous exanthema, or, in very rare cases, intense effects upon the organ of vision, manifested by permanent amaurosis. The usually somewhat inert cod-liver oil may cause vesicular eruptions, iodide of potassium induce hypersecretion from the ocular and nasal mucous membranes, and salicylic acid excite, among other effects, sweating and phenomena of irritation of the nervous system.

Many different designations for the anomalous symptoms produced by drugs are found in literature. In Germany, they were and are still called "*Nebenwirkungen*,"

“physiologische Nebenwirkungen,” “Arzneisymptome,” also accidental, or special, or peculiar effects. French authors designate them “inconvenients,” or “inconvenients thérapeutiques,” also, “accidents,” or “cas d’accidents.” In England, they are sometimes called “accidental poisoning.”

Writers have always hesitated to regard these incidental effects as toxicological, and with justice, for we are not warranted in pronouncing one or more symptoms, which do not appear in a thousand cases after taking a drug, to be the result of poisoning when they show themselves in the next case. It is further to be remembered that the majority of these incidental effects in no wise correspond to the symptoms produced by a poisonous dose of the same drug, and that we cannot produce them at will, especially those affecting the skin. These appear only under definite individual conditions, and are, therefore, almost beyond the reach of experimental provocation. Up to the present time, there has been no lack of physicians thoroughly imbued with humoral-pathological ideas, who, in given cases, attribute a certain teleological significance to the appearance of incidental drug effects, such as was formerly claimed, *e. g.*, for hemorrhage from the hemorrhoidal vessels. In the same manner as it was then regarded as a fortunate circumstance that the “anima” which presided over the vascular system should have chosen the hemorrhoidal vessels for the elimination of “impurities” from the body, were the “drug symptoms,” particularly those affecting the skin, considered as the expression of a struggle between the drug and the morbid humors of the blood, by which the latter, either through functional changes or material anatomical lesions, gave evidence of their subjection or their elimination from the body.

In opposition to this vitalistic humoral-pathological aspect of the subject, another hypothesis has been ad-

vanced to explain the occurrence of incidental drug-effects, as well of those which are the almost constant attendants upon every drug-action, as of those which only occasionally appear. *Their causes may be either peculiar to the individual, or dependent upon temporal or local influences, or the quality of the drug.* The former shall be first considered.

#### § 4.

The peculiarity of each individual, as compared with others, may be permanent or of limited duration. It is most strikingly manifested when the person is exposed to the manifold occasional causes of disease. The same external noxious influence acting upon the organism is capable of producing such different effects upon different individuals, that while some are affected to a scarcely appreciable extent, others are only temporarily injured, and others again experience permanent functional derangements. Individual susceptibility to external influences varies, therefore, within wide limits. It may be so great that causes belonging to the domain of physiology may be capable of producing pathological manifestations. The smelling of a rose, the tasting of a strawberry, etc., may cause in certain persons nervous disturbances or changes in the skin (thus proving the existence of a condition called heightened individual irritability or idiosyncrasy), while the immense majority of persons are in no wise affected by such agencies.

Analogous appearances sometimes show themselves after the external or internal use of certain drugs. The extract of Calabar bean, instilled into the eye, causes in certain persons only a burning sensation in the conjunctival sac and increased lachrymation; morphia, taken internally, causes spasm of the accommodation in excitable subjects only, and pilocarpine, in certain cases and in certain doses, induces profuse sweating, while others, after

the same doses, experience a scarcely perceptible increase of this function. Here we see, under conditions otherwise similar, variations in the influence of external agencies upon homologous tissues, which can only be explained upon the ground of the existence of individual peculiarities.

To the question, what is the nature of these peculiarities? it is impossible to give an entirely satisfactory answer. Only recently have comparative investigations been undertaken into the physical behavior of certain organs, the heart, blood-vessels, intestines, etc., in individuals of different sexes and ages, in the hope of arriving at a comprehension of so-called constitutional peculiarities.

There are furthermore, as we shall see later, a number of physiological processes going on in the body, which render it under certain circumstances peculiarly predisposed to disease, and we are familiar with pathological conditions of so trivial a nature that they pass unrecognized during life, but which render the individual in whom they occur highly susceptible to irritation. But do all these factors suffice to explain "the mystery of individuality," as Virchow calls it? Certainly not! When we recall only a few of the minutiae which must be taken into account, *e. g.*, the infinitely great differences in the distribution of blood-vessels in organs, the multiform arrangement of glandular tissues in glands, the deviations in innervation of organs, the differences in size of individual nerves and in the distribution of nerve-plexuses, the variations in the gross and histological construction of the same muscles in different individuals, we must confess, that not only is our present ignorance great, but that it will always continue. It is nevertheless wrong to entirely ignore the existence of individuality, or to deny its importance. "The possibility of explanation," as Virchow says, "is no test of knowledge, for we know many things empirically whose causes we cannot comprehend. No exact investigation, either anatomical or physiological, patho-



logical or therapeutical, has ever succeeded in lifting the veil which conceals the conditions governing individual peculiarities. In all times it has been regarded as the peculiar prerogative of exceptionally gifted spirits or of great experience to possess that subtle insight which enables one to recognize, even approximately, the specific character of the individual."

It is so well known as to hardly need mention, that since the existence of medicine as a practical and descriptive art, constitutional peculiarities have been appreciated and made the object of investigation. The doctrine of temperaments, the recognition of the sanguine, phlegmatic, and melancholic constitutions, under the hypothesis, that in accordance with the preponderance in the body of the blood, bile, mucus, and black bile, individual peculiarities are established, was for centuries the firm foundation which remained standing after the disappearance of all other medical theories, and although, as the quintessence of humoral pathology, the doctrine is highly one-sided and rests upon a false basis, it is still in complete harmony with the effort to properly appreciate subtle individual peculiarities.

The factors to be considered in the study of the latter cannot be of a gross nature. This is especially true of the specific peculiarities of particular organs. If anything is essentially calculated to support the dictum of Virchow<sup>1</sup> that "the reaction of the tissues does not depend primarily upon external influences, but upon their intimate structure," it is the individual peculiarities which the tissues of certain persons manifest under the influence of drugs. The application of the tincture of iodine to the skin produces usually only an erythema, and yet there are persons upon whom the same preparation causes vesiculation and

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<sup>1</sup> Virchow: Krankheitswesen und Krankheitsursachen. Archiv f. path. Anat., Bd. 79, Heft i., p. 10.

extensive œdema. Even an absolutely inert ointment, made out of any fresh fat, may cause inflammation when rubbed upon the skin of some persons. In such cases, the cause of the unusual effect can only be the existence of subtle alterations in the component parts of the skin, which are physically and chemically unrecognizable. The difficulty of regarding such great functional differences as the consequence of slight variations in the structure of the organ in question, is easily overcome when we consider the differences in the chemical and physical behavior of isomeric bodies, *i. e.*, those which contain the same elements united in the same proportions. In these, a change in the relative position of certain molecules produces so great a difference in their character that they seem essentially distinct from each other. Nevertheless, in them the number of atoms of carbon, hydrogen, and oxygen is always the same, as in pyrogalllic acid and phloroglucin, hydroquinone, resorcin, and pyrocatechin. The behavior of allotropic bodies may here also be recalled. These, probably on account of differences in molecular arrangement, although of identical chemical composition, manifest widely differing physical characteristics, as in the well-known case of carbon in the form of the diamond, graphite, and coal.

It is easy to imagine that certain organs in certain persons are so constituted that, although of the same chemical composition, and even the same histological structure, they are nevertheless so different from others that they respond to a trivial irritation, or show an abnormally intense reaction under ordinary stimulation.

#### § 5.

We have hitherto considered only individuals or organs in their varying relations to others of the same kind. Although the differences which we have thus far found to exist are extraordinarily great, they are nevertheless ex-

ceeded by *those manifested by similar and dissimilar organs in the same individual under the influence of external agencies, especially those of a medicinal nature*, without regard to whether the action is primary, or secondary and reflected.

Even the physiological working power of certain similar organs may be different. The lifting power of a gastrocnemius muscle of one side is seldom, under the same external conditions, identical with that of the muscle of the other side, or the irritability of a nerve equal to that of the corresponding nerve. The explanation of this fact is to be sought in the natural differences in size of the functional elements of the parts, one muscle containing more primitive fibres than its fellow, and one nerve more nerve-fibres than the other, or it may depend upon their relative degree of development. This latter condition may be readily recognized in the greater size of the muscles of the more used right extremities in comparison with those on the left side of the body.

The fact is further to be recognized that similar, but not corresponding portions of the body, as for example, different groups of muscles, may, from the same causes, present differences of action, without being the subject of disease. Thus, a given volume of a deltoid muscle will surpass in working power a similar volume of the intercostal muscles.

We know that while the cardiac branches of the pneumogastric nerve can be excited only by very powerful electric currents, the pulmonary branches of the same nerve show an unusual excitability. Still more striking are the differences between structures into whose formation tissues of different kinds enter, *e. g.*, the joints. One is readily inclined to believe that in this case complete identity exists as regards the arrangement of the individual constituents, and a similarity as regards reaction against external influences. This is, however, not the case. Such complex structures as these, made up, in the instance cited, of muscle, connective tissue, cartilage and bone in widely

varying proportions, and presenting the greatest diversity as regards richness of vascular and nervous supply, are not to be placed in the same category, and are certainly not to be regarded as of equal functional importance.

This is most distinctly manifest, when in diseased conditions of such parts it is desired to produce therapeutic effects upon them by a particular drug. Even when direct applications are made, unexpected differences show themselves. In this connection, an observation of Senator<sup>1</sup> is very instructive. He found that, after the injection of carbolic acid into the joints in acute rheumatism, the beneficial effects appeared first in the shoulder, later in the knee, hand and elbow, and last in the hip. In discussing the subject, Senator mentions as factors probably instrumental in producing these singular results: anatomical differences, the number and arrangement of the vessels, or simply unknown peculiarities of structure of the joints, without, however, being willing to pronounce definitely for the one or the other. The possibilities to be here taken into consideration are so numerous, and we are so far from being able to comprehend even the smallest part of them, that we must content ourselves for the present with studying them with the utmost possible care.

But even if, in a given case, we had demonstrated, *e. g.*, an abnormal arrangement of the vessels of the right shoulder-joint as compared with the left, or a more abundant innervation of the knee than of the elbow-joint, we would still only be able to form a conjecture to explain why the same agent should produce different results when applied to these parts, why it should cure one person and do harm to another.

If this inquiry be still further pursued, it will be found, that in specially predisposed, luckily rarely encountered persons, the simultaneously appearing favorable and unfavorable effects of a drug upon different organs are so

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<sup>1</sup> Senator, Berl. Klin. Wochenschrift, 1876, p. 70

closely connected that the more desirable cannot be obtained without the undesirable. We know of cases in which the employment of iodide of potassium for the purpose of producing a diminution in volume of hyperplastic glands, as the cervical lymphatic or the thyroid, etc., produced the desired effect, and at the same time, a serious atrophy of glands previously healthy, as the mammæ or testes. Such a change can, however, only be due to the fact that those organs, which to our appreciation seemed normal, had already widely departed from the standard of health. Only an abnormality in their intimate structure can allow them to be influenced by an agent which does usually not produce such effects.

### § 6.

The differences thus far considered in the reaction manifested by certain individuals, or single tissues of the same organism, towards certain medicinal influences, were found to depend upon a constitutional predisposition in the economy, either congenital, or acquired and become unalterable.

There is also a predisposition limited as regards time. *This may be due either to the presence in the body in excess, of chemical substances which render more soluble than usual the medicinal agents introduced, or which enter into combination with them, thus forming new and directly deleterious agents, or it may depend upon pre-existing pathological changes in organs, or diseases of the regulatory apparatus.*

With regard to the first explanation, it is well to consider the apposite observations of Mialhe.<sup>1</sup> This author designates the abnormal reaction to medicinal agents due to "differences in composition of the animal fluids," as "chemical idiosyncrasy," as distinguished from "the idiopathic idiosyncrasy," which is to be regarded as the expression of differences in the structure of tissues. It is,

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<sup>1</sup> Mialhe: Die Receptirkunst, übers. von Biefel, Breslau, 1852, p. 239.



for instance, well known that, under some circumstances, insoluble substances, as the oxides of iron, zinc, kermes mineral, etc., may produce in the body effects differing widely from those which usually follow the administration of these drugs, *i. e.*, they may produce injurious effects. The explanation of this is found in the excessive quantity of acid present in the stomach, in consequence of which a larger amount than usual of the metals is dissolved. This difference in the fluids, which may be regarded as the expression of a local disturbance, is entirely distinct from a true humoral-pathological dyscrasia, owing to the fact that it is of a transitory nature, and is often amenable to correction by chemical or dietetic means.

The recognition of the possibility of such a condition of the stomach renders easy, in a given case, the comprehension of certain drug effects. Opinions have differed until now, for instance, as to the reason why the much-used subnitrate of bismuth, even in quite small doses, sometimes causes violent local irritative phenomena in the stomach and intestines, such as vomiting, diarrhœa, etc., as well as general manifestations, while in other cases large doses, 4 to 6 grams, (3 i.—3 iss.) produce no abnormal effects.

It has been definitely established that the presence of lead or arsenic in the bismuth, which was generally believed to be the cause of these untoward results, cannot be so regarded, since they are present in too small quantities. It is much more probable that these effects are due to the quantity of acid present in the stomach. If this be more than normal, the intrinsically harmless basic salt may be converted into the corrosive neutral body, or in consequence of the action of water upon the latter, into the poisonous acid salt, and the absorption of the metal, with its local as well as its general toxic action, be thus rendered possible. That the stomach at different times, according to the individuality of the person, the food consumed, the condition of digestion, etc., may contain different quantities of acid,

is a fact which can be so easily determined clinically and experimentally that it hardly requires further proof.

This is also true of the intestinal juices. The greater or lesser degree of alkalinity which they present is of importance in the solution of a great many mineral and vegetable substances, and when their reaction is only slightly alkaline, a drug-effect may fail entirely or occur in only a slight degree, or, when an opposite condition prevails, so large a quantity of the drug may be dissolved that a modification of the usual curative effect occurs. This latter result is now and then observed to follow the use of the golden sulphuret of antimony. While, as a rule, it produces only a slight expectorant effect, in some cases the full action of the antimony is manifested by the occurrence of vomiting, diarrhœa, and weakness of the heart's action. This can be due only to the fact that an excess of alkali in the intestines dissolves the drug.

Just as great as that of the gastric acid and the intestinal alkali is the influence exerted by the chloride of sodium, which may be present in the body in much more variable quantities than the above-mentioned substances. If calomel be administered, for example, widely-varying effects are produced upon the functions of individual organs, according to the quantity of common salt in the body. In the cases of patients who have been long kept upon a low diet, calomel has almost no effect, because, in consequence of the excessive use of food in a liquid form, the greater part of the chloride of sodium has been already washed out of the body. On the other hand, as Mialhe asserts, persons who have long lived upon a salty diet, as sailors, are peculiarly sensitive to the action of calomel, and may present exceedingly intense local irritative effects in the intestines, as well as a number of other unpleasant effects of mercury.

From these few briefly-described etiological considerations, there result numerous possibilities for the occurrence

of perverse drug-effects. In the majority of them, no special constitutional predisposition is requisite. Pathological alterations in the stomach and intestines, as well as febrile conditions, which exert an influence upon the composition of the secretions of these organs, or even the injudicious consumption of an article of food capable of forming hurtful combinations with certain medicinal agents, may predispose to the occurrence of undesirable incidental effects.

While in this manner alterations may be produced in different parts of the body, wherever the conditions requisite to the formation of products of decomposition are present, certain organs which, at the time of the introduction of certain drugs, are in a pathological state, however trivial, may, for this reason, cause temporarily such a condition of the body that either the already existing alterations are made worse by the medicine, or new pathological symptoms are developed in the same organs, which, in all probability, would not otherwise have appeared. A few illustrations will make this plain. It is well known that iodide of potassium is partially eliminated by the mucous membrane of the air-passages, and that it occasionally causes a slight catarrh of these parts, which usually disappears when the use of the drug is discontinued. If, however, these or other lesions be present before the administration of the remedy, there may be developed, as has been frequently observed, particularly in syphilitic patients with ulcers in the larynx, well-marked œdema of the glottis, which may speedily result fatally. In like manner, very small quantities of drastic cathartics, such as elaterium, gamboge, etc., which, in medicinal doses, occasionally cause transitory, almost physiological, irritative effects in the intestines, may, when the intestinal mucous membrane is in an abnormal condition, produce intense inflammation with its consequences, such as tenesmus, bloody stools, etc. If the

causal relation between such drug-effects and the pre-existing slight organic changes be not understood, it would be easy to erroneously regard the former as a spontaneous disease of the affected organ.

It is scarcely necessary to mention the fact that such conditions as menstruation, pregnancy, mental excitement, intense intellectual effort, and sleeplessness—even the physiological conditions of fasting or digestion—are also capable of modifying the actions of medicines in different ways.

### § 7.

The third cause of a transitory predisposition to the occurrence of unusual drug-effects is found in a disturbance of regulation. When any cause of disease acts upon a part of the body, a disturbance is produced, as Schütz has explained upon the ground of Virchow's teaching. "This disturbance is, however, not pathological, if the regulatory apparatus be in a normal condition. Danger appears only when regulation is difficult or impossible." The good or bad effects of medicines may also depend upon the condition of regulation. The latter is here to be regarded as identical with elimination. Thus, calomel, in a suitable dose, by means of some action upon the intestinal canal, causes an evacuation of the bowels. As soon as this occurs, the greater part of the drug leaves the body with the *fæces*, under the form of sulphate of mercury. But if, for any reason, the cathartic effect does not take place, the calomel may remain in the intestines, especially the *cæcum*, and, by prolonged contact with the chloride of sodium there present, be transformed into corrosive sublimate, and thus produce injurious corrosion with ulceration of the mucous membrane.

If a normal regulation, or, better, a proper performance of function on the part of the usual emunctories takes place, even directly poisonous substances may be taken into the

body without deleterious effects, while evidences of poisoning manifest themselves as soon as one or the other avenue of escape is closed to the drug. Hermann<sup>1</sup> has utilized this fact to explain the intermittent appearance of the symptoms produced by lead. He advanced the hypothesis, "that while lead-cachexia is to be regarded as the effect of the distribution of certain quantities of lead throughout the body, the other symptoms must have a special cause which may disappear in spite of the persistence of lead-poisoning." This cause he finds in a temporary increase in the quantity of lead in the body, either by means of the introduction of a fresh supply, or a diminution in elimination. He designates the condition of saturnism, in which quantities of lead constantly pass through the body, because elimination equals introduction, as "a condition of compensation." It will be readily understood from this "that any diminution of the amount excreted, in consequence of any functional disturbance of the eliminating organs, must temporarily increase the quantity of lead in the body, and so produce new symptoms of an acute character, for the causation of which the usual amount of lead is insufficient." This is also the reason why many persons seem to possess an immunity against the poisonous effects of lead, while others become seriously ill after the introduction of small quantities into the body. It is not even necessary that the channels of elimination should be pathologically altered; for there are conditions comprised within physiological limits which cause interference with the functions of organs; *e. g.*, the kidneys. According to the temperature of the atmosphere, changes occur in the quantity of urine excreted, vicariously with increase or diminution of the perspiration. This is, perhaps, the reason why the great majority of cases of lead colic occur during the hot summer months, when the excretion of

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<sup>1</sup> Hermann, *Archiv f. Anat. u. Phys.*, 1867, p. 64, und *Lehrbuch der Toxikologie*. Berlin, 1874, p. 205.



urine is so much diminished in consequence of the free perspiration.

§ 8.

In order to thoroughly understand certain abnormal effects of drugs, it is necessary, in addition to what has already been advanced, to take into consideration that condition known under the name of *habituation*.

It is well known that, if psychical impressions in their widest range, from the most ardent desire to the most intense aversion, from the greatest joy to the deepest grief operate continuously upon the mind, they gradually lose their influence. The person becomes habituated to them, and the test of their operation, the subjective manifestations which they generally produce, finally cease to show themselves. We are justified in believing that in such cases, the centres of sensibility gradually lose their energy, in consequence of the irritations exercised in such rapid succession upon them, and fail to present the usual evidences of reaction. A readily comprehended analogy for this condition is found in the behavior of muscular tissue towards the electric current. If a muscle be thrown into functional activity by frequent irritation of its nerve, the action continually increases until the maximum capacity of the muscle is reached, and is then succeeded by a stage of exhaustion. This continues as long as the muscle is not allowed to rest, or until time is given to cast off into the blood the products of decomposition resulting from the labor.

Exactly similar conditions obtain in habituation of the system to a number of medicinal agents. Antiquity furnishes us with instances of habituation to poisons. We are told that Mithridates could at last find no poison with which to destroy his life, because he had gradually so accustomed himself to the use of all that were then known, that he could take them in large doses without injurious



effects. Aside from this somewhat doubtful tradition, it is well to call attention to the use of very active agents, such as alcohol, arsenic, opium, and morphine, as practised in our own time by so many persons. The quantity of these substances sometimes taken without apparent injury, by increasing the dose gradually, often amounts to ten or twenty times as much as would certainly prove fatal to a healthy man. Other less active drugs, *e. g.*, many belonging to the class of laxatives and diuretics, entirely lose their characteristic pharmacological effects when too frequently administered. At first the effect may be still produced by increasing the dose, but this becomes impossible finally, even though the quantity of the drug be still gradually augmented. Such results are known, *e. g.*, to be produced by rhubarb, castor oil, the neutral salts such as the acetate of potash, squill, etc.

How are we to explain these peculiar facts? If we suppose any one of these substances to exert its influence upon certain cell-groups in the body, a normal effect will be produced, *e. g.*, sleep will follow the use of morphia, an evacuation from the bowels that of rhubarb. A nerve or a muscle becomes incapable of performing its function under the continued influence of the electric current, on account of the material changes which occur in its substance. A similar result is produced by the action upon the tissues of the body of the above-mentioned drugs. The difference between the two influences is only this, that while on the one hand restitution to the normal condition speedily ensues after the cessation of the electric current, either by elimination of the products of decomposition, or the furnishing of a sufficient supply of new material, on the other hand, after the action of drugs upon organs, a *restitutio ad integrum* can only occur when the foreign substance is in some manner removed from the affected spot. But as the complete elimination of such matters from the body usually requires considerable time, each newly introduced

quantity finds some of the old still present, and therefore the affected groups of cells are exposed to a continuous stimulating or depressing influence. As they are thus deprived of the opportunity for recovery, their functional capacity is lessened, and a physiological or artificial stimulus is therefore no longer able to call forth the usual reaction. It is true that after every further increase in the quantity of the drug administered, an effect is produced, but this condition lasts only until exhaustion of the tissues occurs. If the drug be discontinued, complete recovery may take place, and the same parts eventually react normally to medicines.

The processes above described furnish some insight into the possibility of toleration of certain poisonous substances. In consequence of the gradually increased consumption of such agents, whole cell-groups, particularly those specially affected by the poison, are rendered inactive, still adapted, it is true, to passive vegetative processes, but no longer capable of a definite independent functional activity. The poison acts upon inert tissues, which respond to an excessive dose in the same manner as do normal tissues to one small dose.

Poisonous effects may also be produced even in one habituated to the drug, when it is administered in such large quantities that the vegetative sphere of the tissues is affected and their integrity endangered.

This is, however, not the only way in which abnormal effects may be produced during the persistent habitual use of drugs. It is conceivable, in view of the intimate connection existing between different tissues or organs in the production of the functional manifestations of the body, that the suppression or limitation of the activity of certain parts will be followed by disturbances in the working of such organs as stand in functional connection with them. In this manner a permanent affection of the brain and spinal cord may be followed by alterations in the periphe-

ral nerves, the function of the heart, etc. For this reason, not only a number of more or less intense cerebral symptoms occur in those accustomed to the use of opium, but also disturbances in the functions of digestion, respiration, etc. If the drug be withheld from the body, there appear symptoms which manifest themselves as a disturbance of the previously existing artificial balance in the functions of the individual organs. The most characteristic of these is the persistent craving for the forbidden drug, reminding one of the hunger which is felt for common salt after long abstinence from it. Just as this, an essential constituent of the body, must be supplied, so has the drug, from its habitual use, become an integral element for certain organs, and its omission is resented in the same way as would be that of any other elementary constituent of the body.

Many facts essential to the comprehension of abnormal drug effects result from the considerations just detailed bearing upon habituation. It is plain, *e. g.*, that when the central nervous system performs its functions in an abnormal manner, in consequence of the habitual use of a drug which specially affects it, the action of another agent, which also possesses a special action upon these organs, will be an abnormal one. Either no reaction will occur or it will be manifested in a perverse direction. As instances the action of opium and chloroform on drunkards, particularly in delirium tremens, may be cited.

### § 9.

As an additional and certainly not an unimportant factor in the production of many abnormal effects of drugs, it is necessary to consider the time of the day or year, and the parts of the earth in which they are administered. *Temporal and local influences*, although in general but little attention is now paid to them, even if they do not alone constitute a specific idiosyncrasy in man, contribute largely to its pro-

duction. For this reason, as Virchow<sup>1</sup> says, physicians in ancient times considered man in relation to the time in which he lived, and devoted special attention to "the epidemic constitution." Do we not see that certain morbid influences exert their action only in certain parts of the world, and that at different times the same noxious agency acts with different degrees of intensity upon the body? If individuals are affected by such external agencies, it is easy to understand that certain drugs in a given case may produce manifestations abnormal in kind or degree. Careful clinical observation has led to the discovery of differences in the action of certain drugs in consequence of such influences. Thus Charvet<sup>2</sup> found that the effects of opium differed in accordance with the time of day, the climate, and the race of the subject. Similar observations were often made by physicians in the English colonies. According to the experience of Lisfranc, the medicinal action of the chloride of barium varies greatly in different places, much larger doses being borne in southern than in northern climates.

These facts, whose number might be somewhat increased, are all the more worthy of consideration on the part of physicians because, in this very direction, there prevails a wide-spread, although unfounded, scepticism. We are convinced that careful observation of certain effects of drugs, with regard to these points, would result in the discovery of a large number of similar deviations from the normal.

#### § 10.

In view of the importance which, under given circumstances, may attach to the abnormal or injurious effects of drugs, another fact is to be considered, viz., that *they may*

<sup>1</sup> Virchow, l. c., Bd. vi., p. 29.

<sup>2</sup> Charvet: Die Wirkungen des Opiums auf die th'erische Oekonomie. Leipzig, 1827.

*be due to the quality of the drug used.* It certainly happens much more frequently than is known, or even supposed, that the non-occurrence of a desired result, or the appearance of an undesirable one, is due to an abnormal condition of the drugs or pharmaceutical preparations which have been administered. This abnormality may be due to various causes; *either the drugs* (and this is specially true of vegetable agents) *while in the crude condition were pure but of poor quality, or they were good and became bad because kept too long, or they were sold mixed with foreign substances, or finally, they may obtain unusual qualities in consequence of different methods of preparation.*

It must be remembered that in special cases it is extremely difficult, or even impossible, to distinguish physically and chemically between good and bad drugs, and that very thorough study is necessary in order to enable one to form a judgment in this regard, particularly in the case of animal and vegetable substances.

The variation in the quality of drugs may also be due to the place of their growth. The different kinds of opium, aloes, colocynth, etc., are estimated in trade according to their origin, which is generally the best criterion of the value of a drug. The differences in the modes of action of drugs grown in different places are often very great. While, *e. g.*, abundant stools are produced by 0.06 to 0.12 grams (grs. i.-ij.) of Socotrine aloes, a similar result is rarely obtained by a dose five times as large of Muscat or Arabian aloes. Similar differences are seen in the cases of many of our domestic officinal plants. Thus the digitalis which grows in mountainous regions far surpasses in activity both that which grows in the plains and the cultivated variety. From the hemp cultivated by us no such haschish can be produced as from that grown in hot countries; and hemlock, which with us contains coniine, is in Scotland destitute of this alkaloid. The most diverse factors, character of soil, temperature of atmosphere, season of the year, etc., are

instrumental in causing these differences. The influence of this last factor, in particular, is shown in many of our most active drugs, and has here been definitely determined by accurate observation. We know that even the digitalis which grows in mountainous regions, the Hartz and Black Forest, manifests differences in its pharmacological behavior according to the season in which the leaves are gathered, it being most active when in full bloom. This is also the case with colchicum. It has here also been demonstrated<sup>1</sup> that the roots and seeds gathered while the plants are in blossom are the most active, *i. e.*, contain the greatest proportion of colchicin.

Long preservation causes, in the cases of many drugs, even when they were originally active, changes in constitution, or the formation of new and not uncommonly noxious products. This is the result of desiccation and the oxidizing influence of the air. If, *e. g.*, in the preparation of the extract of hyoscyamus, dry, instead of fresh leaves are used, it will contain almost no hyoscyamin, while the same quantity of leaves from the fresh plant would furnish it in appreciable quantity. *Secale cornutum* loses its power if not sufficiently dried and kept closely sealed. Such a change is most strikingly manifested in the activity of the bark of pomegranate root. While the fresh root possesses most reliable anthelmintic powers, the dried no longer manifests this action, but only produces vomiting or disturbs digestion. There can be no doubt but that a more careful method of treating and preserving drugs than has ever been, or is even now, practised, according to the opinion of those specially skilled in such matters, would have saved many medicinal agents, particularly of the class of vegetables, from the fate of being rejected as inert by physicians.

The influence of the atmosphere causes alterations in

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<sup>1</sup> Schroff, Zeitschrift der Wiener Aerzte, Jahrg. 7, Bd. i., 1851.



many purely vegetable as well as other organic and inorganic combinations. It is well known that, under certain conditions, a number of toxic chlorine products may be formed in chloroform. In the opinion of French authors, morphia acquires its emetic powers by its partial transformation into apomorphia, and it has been proven<sup>1</sup> that Fowler's solution loses arsenious acid in the course of time, probably under the influence of organic substances which have gained access to it. The acid is reduced, and escapes as arseniuretted hydrogen gas. Great loss may be occasioned in this way.

A further occasion for the occurrence of abnormal effects of drugs is furnished by the fact that they are often sold mixed with foreign substances, which may find their way into the mixture during the process of dispensing. Attention has been called to this fact by an expert<sup>2</sup> who has shown that very active substances, such as belladonna root, hellebore root, etc., may sometimes be found mixed with comparatively inert drugs, although in a small proportion, and that special attention to this fact and accurate knowledge of the subject are necessary to avoid the possibility of harm. Finally, as regards the purity of drugs, in so far as this is dependent upon the method of preparation, we know that a number of vegetable alkaloids, aconitine, digitaline, etc., as well as other chemical bodies, produce therapeutical effects, sometimes undesirable ones, varying with the methods employed in their preparations.

In contrast with the variations in the action of drugs above-cited, due to the quality of the remedies employed, we must consider certain effects which may be produced by unsuitable methods of administration. Thus loss of appetite, a feeling of oppression in the stomach, diarrhœa, etc., in short the symptoms of a catarrhal condition of the

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<sup>1</sup> Bretet, *Journ. de Pharm. et Chimie*, October, 1879, p. 355.

<sup>2</sup> Mayer, *Pharmaceutische Centralhalle*, 29th July, 1880.

intestines, sometimes manifest themselves after the exhibition in the form of powder of substances which cause irritation of mucous membranes, in consequence of the adhesion of small particles to the lining membrane of the stomach and intestines. Such symptoms, *e. g.*, may not rarely be traced to the use of tannin in the form of a powder. In a similar manner the administration of irritating drugs in capsules may give rise to functional disturbances in the stomach and intestines.

§ 11.

If a general view be taken of all the influences thus far considered, which may be the causes of injurious incidental effects of drugs, it will be seen from their variety how often they may come into play, and how essential a knowledge of them is. It is true that, as a rule, no permanent functional ill-effects occur in this manner. There are, however, many conditions in which permanent disturbances, even death, may result. It is evident, with this in view, that no slight importance is to be attached to these considerations *from a forensic standpoint*. Foreign and domestic literature bearing upon this point furnishes abundant proof of the truth of this statement. Cases have been published in which the unfavorable result of a therapeutic measure, undertaken with due consideration of the laws of the art, has brought the attending physician into a court of justice, although the same procedure may have often been resorted to by others. For instance, when, after the injection into the rectum of an ordinary dose of a solution of carbolic acid, death follows, owing to some individual peculiarity of the patient, or the patient dies in the beginning of the administration of chloroform, although a pure drug was used, these events are to be regarded as accidents, for which no one can be held responsible. The same remark applies to other drugs which, under certain circumstances, may produce hurtful effects. Well established cases are on

record of death occurring in children after the administration of 0.006, even 0.0007 gram (gr.  $\frac{1}{100}$ — $\frac{1}{1000}$ ) of opium. If the physician were forced to bear the blame in such cases, the administration of such drugs would be attended with grave personal danger. The most complete safeguard against the occurrence of such accidents seems to consist in giving the widest possible publicity to them, in order that a greater amount of information regarding them may be at our disposal than is at present the case.

### § 12.

It remains now to give a general view of the mode of occurrence of the most important incidental effects hitherto recorded in literature of individual drugs. They may be the consequence of a direct or reflex action. In only the smallest number of cases is it possible to determine with absolute certainty in which of these two ways they have been produced, owing partly to the method of application of the remedy, and partly to the manner in which it is eliminated from the body. Thus, it is possible that irritating substances introduced into the stomach may exert an abnormal influence in it or in the intestines, and cause gastrointestinal catarrh, with its results. But, in addition, through the local changes in the stomach, there may be exerted a reflex action upon the functions of the heart, as is the case, *e. g.*, with the preparations of antimony. This does not preclude the possibility of the heart's action being directly affected by the drug after its absorption. This, in fact, sometimes occurs.

It is also conceivable that reflex pathological conditions of the skin may follow an irritation set up by a drug in the intestines or larger bile-ducts,<sup>1</sup> since it is well known that other irritating foreign substances, such as the proglottides of *tæniæ* or gall-stones may by reflex action cause

<sup>1</sup> Litten: Dermatologische Beobachtungen. Charité Annalen, iv., 1878, p. 194.

changes resembling those of urticaria. In an analogous manner, material changes may be produced upon other points of application of a drug, such as the subcutaneous cellular tissue, the mucous membrane of the eye, the bladder or the rectum, and by an action reflected from these, functional disturbances be set up in other organs, and, finally, during the circulation of the substance in the blood, phenomena may occur which differ widely from the primary local and reflex symptoms. The instillation of atropia, for instance, may cause conjunctivitis, and this, by a reflex action, produce photophobia. But, if the drug be absorbed from the lachrymal ducts, symptoms of general poisoning may also appear. However, such a subtle discrimination between these different kinds of effects is, as a rule, impossible.

With regard to the influence of the manner of elimination of remedies in bringing about incidental effects, it should be stated that in this way effects may be produced on different organs, according to the individuality of the patients. We know a number of drugs which are never eliminated from the body by any other channels than the intestines or kidneys, the former when they are taken internally, the latter when administered externally or subcutaneously. But there are drugs, *e. g.*, antimony, which, when applied externally, are first carried into the stomach and intestines, and manifest their action in these organs. Finally, those remedies must be mentioned which usually leave the body with the urine, but, under the influence of any of the abnormal individual conditions detailed in the preceding paragraphs, may, after their internal exhibition, choose the skin as their place of exit, their presence in this organ being chemically demonstrable. As such, among others, may be mentioned iodide of potassium, bromide of potassium, and arsenic. Others, *e. g.*, iodine, may, after injection, be carried into serous cavities and thence into the stomach.

If, as is generally the case, active drugs are used, they may produce irritant or depressing effects upon the organs by which they are eliminated.

Attempts to explain such phenomena have been made most frequently in the case of pathological changes in the skin, following the internal use of certain drugs. To attribute such effects to one cause only, as is now and then done, is apt to lead to errors. It is certain that they may be produced in different ways, and are not exclusively due either to direct irritation of the glands of the skin or the strata of connective tissue, or, through a reflected action, to an alteration in the vessels, or to an influence upon the cutaneous nerves.

It is in all cases the drug, as such, which furnishes the efficient cause for the changes in the skin, whether it be administered in small or large doses. For it is peculiarly characteristic of individuality and the specific disposition which it causes that influences of whatever kind which ordinarily produce no effect, may manifest themselves by causing in different organs changes varying in importance. For this reason, the unfounded hypothesis,<sup>1</sup> that in certain cases, not the drug itself, but certain entirely hypothetical substances formed by it in the blood were the cause of the pathological phenomena, must be absolutely rejected.

The form of a given drug-exanthema may be different in different persons, and may also be multiform in one individual. The differences here manifested must be regarded as the expression of individual peculiarities, or as dependent upon the varying structure of the skin in different parts of the body.

The symptoms produced in the organs of special sense, as well as in other parts of the body, after the use of dif-

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<sup>1</sup> Behrend, Berliner klin. Wochenschrift, 1879, No. 43.

ferent drugs are discussed at length, as regards their genesis, in the special part of this work.

## TONICS.

## FERRUM.

A number of incidental effects may be produced by the long-continued use of iron, principally upon the digestive tract. One observes, not infrequently, in persons with normal digestive powers, after the administration of reduced iron, sulphate of iron and other preparations, and even iron waters, a disturbance of digestion, a feeling of weight in the epigastrium, and vomiting, especially when the remedy is taken upon an empty stomach. Defecation is delayed, and the fæces are colored black by sulphate of iron.

In very rare cases, hemorrhages are said to occur from mucous membranes.

More commonly there appears after the use of iron, as Trousseau<sup>1</sup> states, in healthy individuals, particularly women, an acne, occupying the face, breast, and back, and running its course without the occurrence of fever.

After the prolonged use of this remedy, the teeth are blackened by a deposit of sulphate of iron. But for the production of this result the development of sulphuretted hydrogen, from carious teeth or decomposing secretions, is essential. The iron dissolved in the alkaline fluids of the mouth is at once precipitated by the gas. Even when the teeth are healthy, if articles of food or drink containing tannin are taken, the formation of tannate of iron (ink) may take place.

Regarding the external application of the sesquichloride of iron as a styptic, it is well to call attention to the fact that the pain in the wound which is often caused by it is

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<sup>1</sup> Trousseau, *Gaz. médic. de Paris*, 1843, No. 12.



due to the fact that the preparation used was of a bad quality, since no pain is produced if the iron salt contain no free hydrochloric acid. If it does, the pain is intense, although it soon ceases. What is true of the drug in substance applies also to the styptic cotton found in trade.

In order to make the sesquichloride of iron more easy to take, and to disguise the sour, sharp taste, which does not disappear even after dilution with water, Hager<sup>1</sup> recommends that the drug be mixed with glycerin or simple syrup, and the mixture diluted with cow's milk shortly before taking. He claims that in this way the teeth are not affected, and that the taste of the iron is concealed.

### QUININE.

In explanation of the appearance of injurious incidental effects after the use of quinine, the opinion has been advanced that they are due to a saturation of the organism with the drug. From the very great frequency of these accidents, however, it has been established that sometimes even one small dose is sufficient to produce these effects, and that, therefore, a certain susceptibility to the production of these particular results of the action of quinine must exist in those cases in which they appear. It has indeed been demonstrated by King<sup>2</sup> upon the basis of an observation of this kind, that this individual predisposition to the production of injurious effects by a certain drug, as in this case by quinine, may be hereditary.

The most different organs may be influenced in this manner by quinine, and give evidence of pathological alterations.

On the part of the central nervous system, there are observed headache, deafness, general muscular excitability, sometimes also chilliness and vertigo, disappearing in the

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<sup>1</sup> Hager, *Pharmac. Centralhalle*, 1880, No. 46, p. 408.

<sup>2</sup> King, *Vierteljahrschr. f. Dermat. und Syphilis*, 1879, p. 370.

horizontal position. Occasionally there appear præcordial anxiety, fainting, or symptoms of collapse. Conditions of excitation, delirium, etc., on the other hand, are very seldom observed.

On the part of the circulatory apparatus, the action of quinine is manifested by a diminution of the heart's action, pallor of the face, and coldness of the lips and skin. These phenomena may appear alone, or be attended by one of the affections to be later considered, and may last from hours to days.

*The skin* of many persons is affected in a peculiar manner by the internal use of even small doses of quinine. The eruptions thus produced are characterized by their multiformity. Of importance for the explanation of the occurrence of these affections is an observation first made by Chevallier,<sup>1</sup> and later by other authors, that workmen in quinine factories are exposed, by contact with the drug, to an affection of the skin characterized by the appearance of vesicles, pustules, or papules on different parts of the body, particularly the hands, arms, and legs. This fact goes to prove that when diseases of the skin are caused by the medicinal administration of quinine, they are due solely to the circumstance that the drug is carried into the skin, and by irritating this organ produces lesions varying in extent, probably in accordance with the vascular distribution. Of still greater value for the proof of the correctness of this view than the observation of Chevallier, is a fact experimentally discovered by Munk.<sup>2</sup> When he allowed a current produced by ten Grove's elements to pass through a part of the body, after the electrodes had been moistened with a solution of the sulphate of quinine, the portions of skin acted upon appeared anæmic, dry and depressed, immediately after the interruption of the cur-

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<sup>1</sup> Chevallier, *Annal. d'Hygiène et de Médec. lég.*, 1851, T. 68, p. 5.

<sup>2</sup> Munk, *Archiv f. Anat. und Physiol.*, 1873, Heft 5.

rent. Within the next hour, the same parts became much swollen, so that they projected considerably above the surrounding skin, without, however, undergoing any change in color. The swelling disappeared during the course of several hours, and gave place to a hyperæmia in which there appeared a large number of extravasations of blood no larger than the head of a pin; which remained after the hyperæmia had subsided. Quinine could still be found in the urine twelve hours after the passage of the current. In this case, therefore, in consequence of the passage of quinine through the tissues, an erythema, and later a purpura-like eruption was produced.

Further proof of the local origin of a quinine eruption is furnished by Délioux de Savignac,<sup>1</sup> who saw "a pruriginous eruption" follow the application to the skin of a salve containing the sulphate of quinine.

Similar eruptions have also been observed after the internal use of quinine. These, according to Grissac,<sup>2</sup> appear as:

1. Purpura.
2. Roseola.
3. Scarlatinous exanthema.
4. Eczema.

1. Vépan<sup>3</sup> first observed the *petechial* form. He reports that in the case of a lady suffering from neuralgia, who took first 0.1, later 0.15 gram (gr. ij.-ijj.) of quinine, spots of purpura developed all over the body after two days. They disappeared nine days after the suspension of the remedy, but again showed themselves when its use was recommenced. In this case, the eruption increased in violence and extent with the increase of the dose, and hemor-

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<sup>1</sup> Délioux de Savignac, Article quinine, Dict. encyclop. de Scien. méd., 1874, p. 188.

<sup>2</sup> Grissac: Des éruptions quiniques. Paris, 1876, p. 8.

<sup>3</sup> Vépan, Gazette méd. de Strassbourg, 1865.

rhage took place from the gums while it lasted. Gauchet<sup>1</sup> observed a similar petechial eruption on the person of a lady who had previously suffered from hæmoptysis after taking quinine. The petechiæ were abundantly scattered all over the body, and disappeared on the discontinuance of the remedy.

2. A simple *roseola*, which, however, differs but slightly from the eruption next to be described, has been repeatedly observed by Daubœuf<sup>2</sup> in males and females. It made its appearance attended with intense itching, usually after a number of doses had been taken, in one case even eight days after the last dose was taken. It was sometimes confined to the extremities or trunk, and sometimes spread over the whole body, and usually appeared only in the form of disseminated patches.

3. The *scarlatiniform erythema* was first described by English authors. Garraway<sup>3</sup> saw it appear simultaneously with œdema of the face. In Hemming's case,<sup>4</sup> it appeared after the patient took 0.06 gram (gr. i.) of quinine, was attended with intense itching, a feeling of oppression in the præcordial region, and a coated tongue, and disappeared with slow desquamation. Skinner<sup>5</sup> saw it appear on a lady after 0.06, even 0.03 gram (gr. i.,  $\frac{1}{2}$ ), with shivering and a violent chill. It spread over the whole body, and was followed by desquamation which lasted three months.

The mixed forms of quinine eruptions, a combination of the scarlatiniform erythema and acute eczema in its earliest stage, are next to be considered. Such an eruption was described by Köbner.<sup>6</sup> An eruption which was mistaken for scarlatina, preceded by chills, a feeling of præcordial

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<sup>1</sup> Gauchet, *Bullet. de Thérap.*, lxxxx., p. 373.

<sup>2</sup> Daubœuf, by Grissac, l. c., p. 22.

<sup>3</sup> Garraway, *Brit. Med. Jour.*, 1869, ii., p. 388.

<sup>4</sup> Hemming, *Eod. loco*, p. 533.

<sup>5</sup> Skinner, *Eod. loco*, 1870, i., p. 103.

<sup>6</sup> Köbner, *Berl. klin. Wochenschr.*, 1877, p. 305.

anxiety, nausea, vomiting, and burning on the skin, appeared in the case of a lady after taking 0.22 gram (gr. iv.) of the sulphate of quinine. When the medicine was again administered, the face became slightly bloated, and was covered with a uniform dark redness which spread also over the scalp, ears, neck, and extremities. A few spots of normal skin remained on the arms. The flexor surfaces of the lower third of both thighs were normal, while the extensor surfaces were the seat of isolated papules, of the size of a pea, dark-red in color, becoming pale on pressure. The intervening tissue was healthy, and the epidermis showed fine wrinkling. Heusinger<sup>1</sup> has communicated a somewhat similar observation. A nodular eruption, somewhat similar to erythema exudativum multiforme, appeared in the case of a lady after she took only 0.025 gram (gr.  $\frac{1}{2}$ ) of quinine, on the eyelids, cheeks, and a portion of the forehead, with headache, fever, nausea, a sensation of intense burning and marked œdematous swelling. On another occasion, there appeared in the same case, after 0.1 gram (gr. ii.) of quinine, only herpetic vesicles on the cheeks. The affection disappeared with branny desquamation immediately after the use of the drug was abandoned.

The papules upon an erythematous base may also be transformed into vesicles, and the eruption thus present more of the appearance of an eczema. In this case, the itching may be wanting and the general disturbance be but slight. Thus Denk<sup>2</sup> reports the case of a boy, in which, after the use of 0.8 gram (gr. xiii.) of quinine in four days, an eruption appeared without itching, which extended over the whole body, became pale on pressure, was of a scarlatinous redness, and presented numerous yellow vesicles of pin-head size, most thickly collected on the neck, in the

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<sup>1</sup> Heusinger, Berl. klin. Wochenschr., 1877, p. 361.

<sup>2</sup> Denk, Wiener med. Wochenschr., 1880, p. 946.

axillæ, and over the sternum. The general condition, with the exception of a slight elevation of temperature in the morning and evening, was not affected. After the drug was discontinued, the vesicles began to break and dry up. Desquamation occurred in small scales and large lamellæ.

4. According to Grissac, the appearance of an acute eczema may be still more closely simulated than in the cases just cited, if the numerous vesicles burst and form thick crusts. Such cases are not found in German literature.

In order to distinguish the ordinary quinine exanthema from scarlatina, it is necessary, according to Köbner, to observe the course of the temperature and to find quinine in the urine. Denk adds, as diagnostic points, the absence of the tongue of scarlatina and the inflammation of the palate and tonsils, the fact that the pulse is too slow for the initial stage of scarlet fever, and the sudden appearance of the scarlet redness upon the skin without premonitory symptoms. The presence of quinine in the urine may be demonstrated either by discovering fluorescence in this fluid after it has been freed from chloride of sodium (by precipitating it with nitrate of silver), or by separating the quinine in the form of an iodide by means of a solution of iodine (two parts of iodine, one of iodide of potassium, and forty of water). The iodide of quinine is dissolved on the application of heat.

More unpleasant than the symptoms already mentioned, are the *disturbances in the organs of special sense* observed after the use of quinine.

We shall first consider the disturbances of vision so carefully described by A. von Graefe.<sup>1</sup> After small doses, photophobia, as well as temporary amblyopia, is frequently observed. Under the continued use of larger doses, however,

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<sup>1</sup> Von Graefe, Arch. f. Ophthalmol., Bd. iii., 2, p. 396.



graver disturbances of function occasionally show themselves, which may persist for a long time and obstinately resist treatment. Thus Graefe studied the case of a man who, to cure an intermittent fever, took quinine in increasing doses to 0.9 gram (gr. xiv.) each, or in all about 30 grams (3 viiss.). While the dose was being increased one-third daily, weakness of vision appeared in the right eye, followed in a few days by complete blindness. The left eye remained healthy. Nothing abnormal was revealed by an ophthalmoscopic examination made three months later, but the quantitative appreciation of light had disappeared on the right side. As von Graefe regarded a disturbance of the intracranial circulation as the cause of the affection, blood was drawn from the temple by means of Heurteloup's leech. Quantitative appreciation of light gradually returned first, the motion of the hand could next be appreciated, and after some time the eye returned to its normal condition. In another case, in which 1.8 gram (gr. xxviii.) of the sulphate of quinine was taken daily, also for the cure of intermittent fever, and in which bilateral amblyopia of a high degree appeared, the full power of vision returned spontaneously in the left eye, but the right regained only the power to read large print.

The ear may be functionally affected in the same way as the eye, and its disturbances may appear with varying intensity either simultaneously with the affection of the eye or independently of it. Very frequently, as the mildest form of the affection, appearing at the same time as other nervous disturbances, only a buzzing or ringing in one or both ears is observed; but later difficulty of hearing, and even deafness may also appear. According to Briquet,<sup>1</sup> these symptoms, in most cases, last only a short time. On the other hand, Bailly<sup>2</sup> states that incurable deafness may follow the use of quinine.

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<sup>1</sup> Briquet : *Traité Thérapeut. de Quinquina et de ses préparats.* Paris, 1853.

<sup>2</sup> Bailly, *Gazette méd. de Paris*, 1850, 9.

It must also be mentioned that stomach and intestinal catarrhs of different grades of intensity are produced with tolerable frequency by the use of quinine. For this reason, Binz<sup>1</sup> warns against the introduction into the stomachs of patients with fever, of quinia salts which are not easily dissolved. Quinine in a slightly acid solution is readily absorbed, and may be taken for weeks without injury; but quinine in powder or pill form, especially the almost insoluble sulphate, may, on account of the lack of gastric acid which probably exists in persons with fever, easily produce irritation in the stomach and intestines.

It has been further observed by Guyochin<sup>2</sup> that, after the use of quinine, slight irritation of the kidneys and the mucous membranes of the bladder and urethra may occur, probably owing to the direct contact of the drug with these parts. Faginoli<sup>3</sup> treated a child, who suffered from painful micturition, and passed a few drops of blood every time it took quinine. Monneret saw a genuine hæmaturia arise in this manner. Piorry and Briquet also claim, in very rare cases, to have observed symptoms of cystitis following the use of quinine.

In the case of Gauchet reported above, we have mentioned a symptom which is very rarely alluded to in the literature of quinine, viz., hæmoptysis. Simon de Ronchard<sup>4</sup> was the first to observe several cases of spitting of blood after daily doses of quinine of 0.5 gram (gr. viij.). The affected persons had healthy lungs and hearts. As soon as the drug was discontinued the hæmoptysis ceased, but blood again made its appearance in the sputa when it was again used. How this effect of quinine

<sup>1</sup> Binz, *Deutsche Klinik*, 46, p. 409.

<sup>2</sup> Guyochin: *Absorption, Action physiologique et thérapeutique de la Quinine*, Paris, 1872.

<sup>3</sup> Faginoli, by Grissac, *l. c.*, p. 43.

<sup>4</sup> Simon de Ronchard, *Gazette des hôpitaux*, Janvier, 1861.

occurs has not yet been explained. It has, however, been established by the investigations of Mérat that, after the internal use of quinine, the drug may be found in the bronchial mucus.

Therapeutic measures are but rarely necessary against such symptoms as have been detailed, since they disappear spontaneously after the discontinuance of the drug. For the relief of the conditions of weakness which have been described, symptomatic 'tonics are to be employed if they become excessive.

To prevent the headaches which so frequently appear, Wade<sup>1</sup> recommends hydrobromic acid. Fothergill experimented with this drug, and was able to confirm its reputed efficacy. He prescribed two to twelve grams (fl. 3 ss. to fl. 3 iij.) diluted with water, of the acid obtained by precipitating a solution of forty-seven parts of bromide of potassium in three hundred and fifty parts of water with fifty-eight parts of tartaric acid.

Rapid disappearance of the quinine eruption was noticed by Lightfoot<sup>2</sup> to follow the administration of twenty-five drops of the tincture of hyoscyamus and sponging the body with alkalies. Heusinger (i. c.) had the affected portions of skin powdered with wheat-flour.

#### SALICYLIC ACID—SALICYLATE OF SODIUM.

Salicylic acid is to be classed with the drugs which most frequently and extensively produce undesired effects. Some of this class of symptoms seem to be typical attendants upon the anti-febrile action of the drug, and therefore very frequently follow its use. In this category belong certain phenomena, yet to be considered, manifested by the central nervous system.

Other symptoms, such as changes on the skin and dis-

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<sup>1</sup> Wade, Ref. Virchow-Hirsch Jahresber., 1876, i., p. 400.

<sup>2</sup> Lightfoot, Brit. Med. Jour., 1870, i., p. 30.

turbances of the functions of internal organs, appear but seldom, and are probably dependent upon an individual predisposition on the part of the affected patient. They all have this in common, that they disappear rapidly without leaving injurious results behind.

On taking salicylic acid, there is experienced a repulsive taste, with burning and itching in the mouth and throat. After absorption, as Stricker<sup>1</sup> first stated, there may occur buzzing in the ears, difficulty of hearing, and profuse sweating—symptoms which do not contra-indicate the continued use of the drug. Still more important nervous symptoms have been observed by other authors. Thus, Riegel,<sup>2</sup> after doses of four to six grams (3 i. to 3 iss.), noticed, in addition to the above-mentioned symptoms, headache, giddiness, and very temporary delirium, and Schuhmacher,<sup>3</sup> in addition to these, observed hallucinations of visions which caused great anxiety. According to Riess,<sup>4</sup> besides this condition of psychical excitation, there may appear weakness of vision, as well as specks before the eyes. Müller<sup>5</sup> observed, on the other hand, after the daily use for nine days of fifteen grams (3 ss.) of salicylate of sodium, in a case of diabetes, a condition of psychical depression, with violent headache and mental weakness, and, at the same time, peculiar motor disturbances. The patient complained of weakness in the legs, uncertainty of motion, a paretic inclination of the body to the right side, and also that, although his sight was good, he ran against objects while walking. The symptoms disappeared within five days after the use of the drug was discontinued, and reappeared when it was again taken in smaller doses.

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<sup>1</sup> Stricker, Berl. klin. Wochenschr, 1876, No. 8.

<sup>2</sup> Riegel, Berl. klin. Wochenschr., 1876, 182.

<sup>3</sup> Schuhmacher, Deutsche med. Wochenschr., 1876, No. 18.

<sup>4</sup> Riess, Berl. klin. Wochenschr., 1875, p. 675.

<sup>5</sup> Müller, Berl. klin. Wochenschr., 1877, p. 29.

Goltdammer<sup>1</sup> observed conditions of collapse of different degrees several times after small doses, five grams (gr. lxxv.), of salicylate of sodium.

No investigations have as yet been made as to the manner of occurrence of these symptoms, which bear a certain resemblance to those produced by quinine. They are probably the expression of the direct action of the drug upon certain parts of the brain.

Among functional disturbances of internal organs, those which affect the stomach and intestines are first to be considered. There exists an isolated observation of Goltdammer, who, after the administration of twelve grams (3 iij.) of salicylic acid to a patient with acute miliary tuberculosis, found after death a number of deep ulcerations of the size of a pea, on the mucous membranes of these organs. These he attributed to hemorrhagic erosions, probably due to the irritating quality of the drug.

In opposition to this view, Riegel (l. c.) states that, after four to six grams (3 i. to 3 iss.) doses of the drug, he could never find changes in the mucous membrane of the œsophagus, stomach or intestines. Nevertheless, cases have been reported by different observers, in which, after the use of salicylic acid and salicylate of sodium, pain was felt in the stomach, with vomiting and diarrhœa.

It would seem that the drug, under certain circumstances, although rarely, is capable of causing irritation of the kidneys. Lürmann<sup>2</sup> reports the occurrence, after taking four grams (3 i.) of salicylate of sodium, of albuminuria, with œdema of both forearms and legs, which ceased when the drug was stopped, and reappeared when it was again administered. After larger doses, Müller (l. c.) also witnessed the occurrence of diminution in the amount of urine, and albuminuria.

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<sup>1</sup> Goltdammer, Berl. klin. Wochenschr., 1876, p. 47.

<sup>2</sup> Lürmann, Berl. klin. Wochenschr., 1876, p. 477.



It still remains to consider the changes in the skin occasionally observed after the use of salicylate of sodium. These generally appear as erythema or urticaria, or in a petechial form, and are usually attended with intense itching.

After four grams (3 i.) of the drug, Heinlein<sup>1</sup> witnessed, in a case of articular rheumatism, the appearance, accompanied by unbearable itching, of a diffuse redness of the left half of the face, the lower extremities, and the right side of the chest, with slight œdema of both eyelids, the upper lip, and the legs as far as the middle of the thighs. All these symptoms disappeared within twenty-four hours after the discontinuance of the drug. When four grams (3 i.) of the salt were again administered, there appeared a diffuse erythematous redness, with itching, while the whole abdomen, as well as the lower extremities, became covered with wheals seated upon a reddened base. The latter disappeared spontaneously after an hour, the other manifestations on the following day. Leube also saw an urticaria appear after four grams (3 i.) of salicylate of sodium. Freudenberg<sup>2</sup> saw a petechial eruption in an individual suffering from marasmus, after five grams (gr. lxxv.) of salicylate of sodium were taken daily for five days. The petechiæ, which were the seat of intense itching, and some of which were as large as a half-dollar, were originally seated upon the back, but spread on the following day over the breast, shoulders, upper arms, hips, and thighs. In the course of eight days, the spots became paler, and the epidermis was cast off in great scales from the affected parts. After complete recovery, five grams (gr. lxxv.) of salicylic acid were administered in capsules, with a similar result.

#### RESORCIN.

This drug, but recently introduced into the materia

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<sup>1</sup> Heinlein, *Aerzt. Intelligenzblatt*, April, 1878.

<sup>2</sup> Freudenberg, *Berl. klin. Wochenschr.*, 1878, p. 630.



medica, produces, like other antifebrile remedies, when administered in active doses, incidental effects, especially upon the central nervous system. Lichtheim<sup>1</sup> and Brieger<sup>2</sup> have reported observations bearing upon this point.

If two or three grams (gr. xxx. to xlv.) of resorcin are administered in solution or in substance, an effect is manifested in a very few minutes. There appear giddiness, buzzing in the ears, and an increase in the frequency of pulse and respiration. The face is reddened and the eyes become brilliant, the patients being in a condition resembling intoxication. They are sometimes delirious, and manifest hallucinations. Speech is stammering, and slight convulsive tremors appear in the hands.

Soon after taking the drug, the skin becomes moist, and in 15 to 20 minutes profuse sweating occurs. At the same time, the temperature of the body falls, and the above-described symptoms of excitation diminish in intensity. Brieger saw collapse occur in this stage, which so increased with the diminution of temperature, that powerful stimulants had to be frequently employed. The fall in temperature lasted only a short time. After two or three hours, fever abruptly appeared, with a feeling of coolness or even a chill.

#### STRYCHNIA.

Strychnia, even in permissible doses, may produce a chain of threatening symptoms, differing only in degree from true strychnine poisoning. After 0.005, 0.01 gram (gr.  $\frac{1}{20}$ — $\frac{1}{10}$ ) of strychnine, there may appear nausea, redness of the eyes, formication, exalted sensibility to external impressions, a feeling of weight in the feet, and stiffness in the limbs. With these symptoms are occasionally associated disagreeable tension of certain groups of mus-

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<sup>1</sup> Lichtheim, *Correspondenzblatt f. schweizer Aerzte*, 1880, 14, 15 Juli.

<sup>2</sup> Brieger, *Centralbl. f. med. Wissenschaft*, 1880, 37.

cles, and painful erections. Girl<sup>1</sup> several times observed, after the repeated internal administration of strychnia, the occurrence of periodic spasmodic attacks, reappearing during the course of several weeks, of a tertian type, resembling an intermittent fever, and ending with sweating. After they had ceased, they could be reproduced by strychnia.

Children are specially susceptible to the injurious effects of strychnia, and for them it must be prescribed with extreme caution. A number of cases have been observed of severe, even fatal, poisoning by medicinal doses of the drug administered subcutaneously for the relief of diphtheritic paralysis.

A skin affection produced by the internal administration of strychnia has also been described. In the case of a woman who took 0.0004 gram (gr.  $\frac{1}{1600}$ ) of the drug, Skinner<sup>2</sup> saw a scarlatinous exanthema, which disappeared after it was discontinued.

#### COLOMBO ROOT.

The Colombo root, so much prescribed as a bitter and astringent, probably contains as its active principle berberine and the crystalline bitter substance colombine. As shown by an experiment of Köhler<sup>3</sup> upon himself, with an infusion of twenty grams to one hundred and twenty grams of water, a certain amount of care should be taken in the use of this drug. It produced nausea, repeated vomiting, pain in the epigastrium, and finally unconsciousness after the subsidence of which a condition resembling that following a debauch remained. All these symptoms had disappeared after twenty-four hours. For this reason, it seems advisable, until more accurate pharmacological in-

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<sup>1</sup> Girl, Buchner's Repertorium, xxi., 2.

<sup>2</sup> Skinner, British Med. Jour., 1870, p. 303.

<sup>3</sup> Köhler: Handbuch d. physiol. Therapeutik, 1876, p. 159.

vestigations of this substance are at hand, to prescribe it only in small doses, rather than as is now the custom. Probably in this way only the bitter principle exerts the main action, and in larger doses the alkaloid berberine.

#### LIGNUM QUASSIÆ.

Quassia wood, which is an intense poison to the lower insects, produces no functional disturbances when occasionally taken in small doses as a stomachic. But when taken for a long time or in large doses, it produces digestive disturbances in some persons, which may be accompanied by oppression in the stomach, nausea, and inclination to vomit. Furthermore, according to Wibmer,<sup>1</sup> in children and delicate adults, dizziness, headache, and deafness may be produced by large doses. Barbier saw in sensitive women involuntary muscular movements follow the use of a watery solution of quassia wood.

#### HERBA CHELIDONII.

Celandine, which was formerly regarded as a specific for affections of the liver, exerts an action only when freshly gathered. The herb then contains a yellow juice which may cause an irritation of the skin with the formation of vesicles. Taken internally in small doses, it may cause nausea and an inclination to vomit, vomiting or diarrhœa, and headache. It is said that, after its external use, there sometimes appear papular or vesicular eruptions on different parts of the body, especially the face.

#### CREASOTUM.

After the long-continued internal use of creosote in the treatment of diarrhœa, there appear, as Richardson found, dryness in the mouth, a burning sensation extending from the pharynx to the stomach, a white membraniform coating

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<sup>1</sup> Wibmer: Die Wirkungen der Arzneimittel und Gifte. Munich, 1842, Bd. iv., p. 380.

of the tongue, and increased frequency of the pulse. In rare cases, vomiting and increased frequency of micturition also occur, attended with persistent headache.

An affection of the skin has also been observed after taking creosote. M. Bernard<sup>1</sup> saw in the case of a lady, no matter in what form he prescribed the drug, an eruption attended with violent itching, which proved to be urticaria. It disappeared after stopping the medicine, and reappeared when its use was again begun.

After the external application of this drug for caries of the teeth, there may appear a stomatitis and swelling of the tongue, if it comes in contact with this organ and the gums.

When incidental effects make their appearance during the internal use of creosote, it must be at once discontinued, and if gastric disturbance be present, demulcent drinks should be prescribed symptomatically. The local affections of the mouth soon disappear spontaneously, or yield to an antiphlogistic or astringent treatment.

#### OLEUM TEREBINTHINÆ.

The oil of turpentine, obtained by distillation with water from turpentine, the resinous juice of several varieties of fir, used either internally or externally in varying doses, produces in some persons a number of undesirable incidental effects which, in some cases, may render its further use unadvisable.

After the application of the drug to the uninjured skin, erythematous changes, sometimes even vesicular eruptions, appear, with a feeling of warmth and itching. They soon pass off when the drug is discontinued. Upon the surfaces of wounds the action is very intense and may cause extensive inflammation. The vapor of turpentine, also, may produce a burning and itching erythema, as proved

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<sup>1</sup> M. Bernard, *Gazette des hôpitaux*, 1879, p. 170.

by the employment of turpentine vapor-baths in the treatment of rheumatism, as recommended by Chevandier.<sup>1</sup> In animals, the effect upon the skin is manifested by falling of the hair.

Schlothauer<sup>2</sup> also observed the appearance of intense salivation and stomatitis after one application of turpentine for the cure of scabies. This result of the absorption of the drug is in all probability due to a reflex excitation of the salivary secretion in consequence of an irritation of the buccal mucous membrane by the turpentine eliminated with the expired air, since the introduction of the drug into the mouth also may cause an increase in the flow of saliva and redness of the mucous membrane.

*The internal use* of the oil of turpentine resorted to, as is well known, in a large number of affections, such as neuralgias, phosphorus poisoning, and colic from gall-stones, frequently causes many accidental effects, which may be intensified to a dangerous degree. Thus, after small doses, one occasionally observes burning in the primæ viæ, the formation of vesicles in the mouth, pains in the epigastric region, diarrhœa with colicky pains, and vesical tenesmus, leading to the discharge of an increased quantity of urine usually with an odor of violets, and sometimes bloody. With the irritation of the kidneys there may be associated redness of the urethral mucous membrane and painful erections.

After the repeated use of medicinal doses of the oil of turpentine, an effect upon the central nervous system is not unfrequently produced, manifested by headache, giddiness, and a feeling of fulness. Purkinje,<sup>3</sup> who took each morning for 3 days 4 grams (3 i.) of the oil, became sleepy after it, and could keep awake only with difficulty; capa-

<sup>1</sup> Chevandier, *Revue Medico-chirurg.*, 1851.

<sup>2</sup> Schlothauer, *Medic. Zeitung des Vereins für Heilkunde*, 25 Juni, 1851.

<sup>3</sup> Purkinje, *Ref. in Mitscherlich's Lehrb. der Arzneimittellehre*, Bd. ii., p.

city for thought and power of motion remained intact. The occurrence of these symptoms may be partially explained, since Rossbach and Fleischmann<sup>1</sup> have shown that turpentine possesses the power to diminish the excitability of the central nervous system. Similar effects, due to a general action of the drug, may be produced by the extensive external application of the oil of turpentine.

It is finally to be mentioned that, as after its external application, changes in the skin sometimes occur after its internal use also. According to Béranguier,<sup>2</sup> after comparatively large doses, there appears a simple scarlatina-like erythema, spreading by preference over the face and the upper part of the body in irregular patches. Sometimes there appears upon the reddened surfaces, with itching, a large number of small papules, which give to the skin an eczematous appearance. In rare cases, a vesicular eruption is noticed. A number of such cases have been reported by Brochin,<sup>3</sup> in which erythema or an urticaria-like eruption always showed itself in certain persons after the administration of turpentine, either in solution or in capsules or in a pure state.

#### BALSAMUM COPAIBÆ.

After the use of balsam of copaiba, generally after the first day, seldom after the eighth, certain affections of the skin appear in certain persons, usually suddenly. They were first described by Montègre (1817). In the majority of such cases, only a roseola is observed in the beginning. The rose-red irregular spots may, however, be transformed into true papules, projecting above the skin. Now and then the eruption is papular from the start, but, according

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<sup>1</sup> Rossbach and Fleischmann: *Pharmak. Untersuchungen aus dem Würzburg Instit.*, Bd. iii.

<sup>2</sup> Béranguier: *Des éruptions provoquées par l'ingestion des médicaments*. Paris, 1874.

<sup>3</sup> Brochin, *Gaz. des hôpitaux*, 1879, Fév., p. 99.



to Bazin,<sup>1</sup> it differs somewhat from an ordinary febrile urticaria. Gubler and Rayer have described miliary and scarlatina-like eruptions, and also an eczema, as sometimes following the use of copaiba, although very rarely. These appear by preference upon the upper and lower extremities, especially the backs of the hands, the knees, and around the malleoli and upon the breast, and sometimes spread over the whole body, and are occasionally attended with tolerably high fever. According to Béranguier,<sup>2</sup> the roseola produced by balsam of copaiba sometimes bears a striking resemblance to a papular syphilide, but is distinguished from it by its sudden appearance, the presence of itching, by its affecting by preference the above-mentioned parts of the body, and by a peculiar disagreeable odor of the skin, and especially by the fact that it disappears when the use of the drug is discontinued.

The eruption is attended with intense itching. The spots or papules are either isolated or collected in groups, and in the latter case they may form patches of considerable size. They disappear upon pressure, and return when it is removed. If the use of the drug be discontinued after the appearance of the eruption, the latter may either disappear in 1 or 2 days, without desquamation, or, in accordance with the individuality of the patient, or the length of time during which the drug was taken, this may require from 1 to 3 weeks. Under continued use of the drug, the eruption may be transformed into a more severe form, and even involve the subcutaneous tissue.

With reference to a statement of Hardy<sup>3</sup> who saw a pemphigus-like eruption after the use of copaiba, Hebra<sup>4</sup> calls attention to the fact that the eruption was probably not a pemphigus, but only an urticaria, and that the ser-

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<sup>1</sup> Bazin : *Leçons sur les affections cutanées artif.* Paris, 1862, p. 184.

<sup>2</sup> Béranguier, *l. c.*, p. 22.

<sup>3</sup> Hardy, *Gazette des hôpitaux*, 1869.

<sup>4</sup> Hebra: *Hautkrankheiten*, i., p. 673.

ous infiltration of the layers of the epidermis, which causes the wheals of the latter, need only be present in a more intense degree in order to produce a bulla.

Balsam of copaiba also acts injuriously upon various mucous membranes, even in not excessive doses, when long used. There is not unfrequently observed loss of appetite, a feeling of weight in the stomach, nausea and vomiting, and also, according to Bazin (l. c.), hyperæmia of the conjunctiva and the pharynx, as well as irritation of the kidneys and bladder, sometimes resulting in the production of nephritis and cystitis.

The manner in which these effects are produced is clear. Like other resinous substances, balsam of copaiba produces a tolerably intense irritation of mucous membranes, probably through the oil of copaiba or the copaibic acid which it contains. Elimination takes place through the lungs, as well as the kidneys, and therefore the urinary passages may be irritated in proportion to the quantity of the balsam passing through them. The skin may also serve as a point of exit for the drug, and, therefore, this organ or its glands may be the starting-point of inflammatory processes. In how far, in different persons, an abnormality in vascular distribution, or a peculiar condition of the glandular elements of the skin may contribute to the production of such effects, has not yet been determined. The fact is, however, established that, after the use of balsam of copaiba, the skin frequently emits a peculiar odor, probably due to volatile products of decomposition of the drug, and that in such cases the curative powers of the drug in gonorrhœa are very slight.

It should be stated that the urine passed during the use of balsam of copaiba furnishes a deposit with nitric acid, which consists of copaibic acid, and may easily be confounded with albumen.

Maestri and Pidoux<sup>1</sup> report that large doses of balsam of copaiba sometimes cause symptoms of poisoning, such as paralyses with convulsions and tetanic symptoms. In milder cases, there may appear weakness of the arms and the muscles of the face, with diminution of the general sensibility.

#### CUBEÆ.

As a rule, incidental effects do not follow the use of cubebs. In some persons it produces colicky pains and diarrhœa.

An eruption is usually produced only by large doses, and in the cases of young persons. It is characterized either as an erythema or more frequently a papular eruption, which, as in a case reported by Béranguier (l. c.), spreads over the face, the trunk, arms, and legs. The papules are miliary, but unite in many places to form large elevations above the skin. The eruption appears without attending symptoms, such as fever, etc., and disappears in a few days, after the discontinuance of the drug, with slight branny desquamation.

#### AQUA CALCIS.

The continued use of lime-water, in consequence of the persistent neutralization of the gastric acid, not unfrequently causes disturbances of digestion and loss of appetite; vomiting has also been observed to follow its use. The excretion of urine is increased by this remedy, defecation is usually retarded, and in rare cases diarrhœa is produced.

In order to avoid these evils, it has been proposed to use saccharate of lime, in doses of 0.5–1 gram (gr. viij.–xv.), in watery solution, instead of lime-water.

The above remarks are also applicable to the carbonate of lime.

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<sup>1</sup> Maestri and Pidoux, Ref. Schm'idt's Jahrbücher, Bd. 97, p. 301.

## SODII NITRAS.

After the use for some time of large, but still medicinal, doses of the nitrate of sodium, Löffler<sup>1</sup> observed certain changes in the persons who had taken the drug as an experiment. Twice there appeared pain and rumbling in the abdomen. Digestion was, as a rule, not at all affected by the drug. But, increasing with the quantity of the drug consumed, there appeared a feeling of general lassitude, increased on motion, and lasting several days after the discontinuance of the drug, disinclination to bodily and mental activity, depression of spirits, a tired feeling after the slightest exertion, pains in the muscles and joints, particularly in the knees, and a continuous inclination to sleep.

The quantity of urea is increased during the first few days of the administration of the drug, but afterwards returns to, or even falls below, the normal standard.

## ADSTRINGENTIA.

## ALUMEN.

After the frequent use of alum, there are observed in some persons gastric symptoms, such as loss of appetite, nausea, a tendency to vomit, and diarrhœa. These effects are due to a direct irritation of the gastro-intestinal mucous membrane by the drug, and are dependent upon the degree of fulness of the stomach. For if the alum introduced into this organ does not meet with enough albumen or albuminoid substances to precipitate it, the mucous membrane is affected by the drug in a greater or lesser degree.

In the experience of Bégin and also of Barbier, the long-continued use of small doses of alum sometimes produces cough in persons with sensitive bronchial tubes.

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<sup>1</sup> Löffler in Barth, *Toxikologische Untersuchungen des Chilisalpeters*. Bonn, 1879, p. 5.

## BISMUTHI SUBNITRAS.

Perhaps in the case of no other drug do opinions as to its eventual hurtfulness or innocuousness differ so widely as in that of subnitrate of bismuth. While Monneret,<sup>1</sup> among others, assures us that the irritating or even poisonous qualities which have been attributed to this substance are only imaginary, that it may be taken by patients to the extent of three to six teaspoonfuls daily without any inconvenience, and that it can act curatively only in such large doses, there is a large number of reliable observations which go to prove that subnitrate of bismuth in medicinal doses [2 to 4 grams (gr. xxx. to 3 j.) daily], may sometimes produce hurtful effects. The attempt has been made to explain these contradictory statements, by regarding the impurity of the preparation used, particularly its admixture with lead or arsenic, as the cause of the undesirable incidental effects. In fact, Carnot,<sup>2</sup> among others, in all the specimens of subnitrate of bismuth which he examined, found lead in quantities varying from 1 to 10 per cent. Riche,<sup>3</sup> on the other hand, found it in a much smaller proportion, and states that the quantities of this metal discovered by him were too small to cause disturbances in the organism. In fact, Bouchut<sup>4</sup> regards the presence of lead as beneficial, claiming that it is this substance which enables the bismuth to exert its curative action in diarrhœa.

The proportion of arsenic found in bismuth is also too small to produce the symptoms soon to be detailed. The anomalous effects of the agent must, therefore, be ascribed to the temporary condition of the individual who reacts

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<sup>1</sup> Monneret, *Centralzeitung*, 1849, 43.

<sup>2</sup> Carnot, *Comptes rend. des Séances de l'Académie des sciences*, T. lxxxvi., p. 118, 1878.

<sup>3</sup> Riche, *Jour. de Pharm. et Chimie*, 1878, 28, p. 147.

<sup>4</sup> Bouchut : *Jahresb. über Pharmakog. u. Toxikol. von Dragendorff*, 1879, p. 268.

abnormally under its use, or to its employment in an improper manner.

The condition of the individual may be influential in so far as the presence in the stomach of greater quantities of acid may cause the formation in large quantities, from the subnitrate of bismuth, of the corrosive neutral salt, or, if this be decomposed by water, of the acid salt. These are, however, as Orfila<sup>1</sup> proved by experiments on animals, intense poisons, producing gastro-enteritis. The same changes would take place if the basic salt were administered at the same time with acid remedies, or if the patient should take acid substances after the salt. In this manner, the readily soluble nitrate of bismuth, which would be formed in the stomach, would be absorbed.

The incidental effects observed after the use of subnitrate of bismuth are almost identical with the pathological phenomena which are characteristic of the action of the acid salt, and affect principally the stomach and intestines. Odier<sup>2</sup> saw nausea after its use, Werneck<sup>3</sup> vomiting, colicky pains, and, in some cases, diarrhœa, in others, obstinate constipation. With these local symptoms were associated a feeling of heat, headache, dizziness, and general lassitude. It is especially worthy of remark that the stools, after the use of subnitrate of bismuth, are generally of a grayish-black color, and almost odorless. This is due to the fact that the bismuth salt is transformed in the intestine, under the influence of sulphuretted hydrogen gas, into the sulphate of bismuth, and the gas is thus held fast.

The therapeutical indications against the above-mentioned incidental effects are the discontinuance of the drug, and the occasional employment of calcined magnesia in small doses, or of milk, emulsions, etc.

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<sup>1</sup> Orfila : *Toxikologie*, übers. v. Krupp, 1854, ii., p. 9.

<sup>2</sup> Odier, *Jour. de Médecine*, 1768, T. 68, p. 49.

<sup>3</sup> Werneck by Wibmer : *Wirkungen d. Arzneimittel*, T. 1, p. 418.



## ACIDUM BORACICUM.

According to the investigations of Binswanger,<sup>1</sup> boracic acid in medicinal doses exerts no action in the human organism. If the dose be increased to two or four grams (grs. xxx.-lx.), there may occur frequent desire to micturate, and an increase in the quantity of urine. In one case, after six grams (3 iss.) daily, forty-five minutes after taking the second dose, nausea and vomiting occurred.

No incidental effects have as yet been observed after the external application of boracic acid.

## ARGENTI NITRAS.

The changes which silver produces by its long-continued external or internal use, consist in a discoloration of the tissues in consequence of a deposition of the metal in them. Secondarily, as an effect of the presence of this foreign substance, functional disturbances may be developed in different organs.

The alterations in the tissues have been frequently made the subject of microscopical investigations. Virchow<sup>2</sup> examined a portion of the conjunctiva of a man for whom a solution of nitrate of silver had been prescribed as an application to the eye, which he had, by mistake, used continuously for four months. The conjunctiva presented an intense bluish, almost black appearance. A deposition of the silver in its substance had taken place, "in such a manner, that on the surface the connective tissue was of a light brownish-yellow color, and in the deeper portions, the deposit had occurred only in the fine elastic fibres or corpuscles of the connective tissue." The basis-, or intercellular substance itself, was normal.

That the healthy skin may also be the point of entrance

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<sup>1</sup> Binswanger: *Pharmakolog. Wirkungen der Borsäure und des Borax*, München, 1847.

<sup>2</sup> Virchow: *Cellularpathologie*, 1871, p. 250.

of the silver is proved by the case of a woman reported by Gamberini.<sup>1</sup> This person, in order to dye her hair black, rubbed it every two weeks, for a period of two and a half years, with a pomade containing nitrate of silver. She afterwards suffered from dyspnœa, palpitation of the heart, ascites, and œdema of the legs, after the disappearance of which last symptom, the skin became of a slaty-gray or light-brown color.

The recommendation of nitrate of silver for the treatment of epilepsy, tabes dorsalis, and similar diseases, has, in consequence of the chronicity of these affections, led to the long-continued use of the drug, and this has frequently produced that condition of deposition of silver in the tissues known as arguria, with its consequences. It is stated that thirty grams (3 viiss.) is the smallest quantity of silver which has been known to produce this condition. The discoloration may affect the whole cutaneous surface equally, or be most intense in certain parts, as the face. Scars, nails, and hair may also experience changes in color.

Functional disturbances are frequently manifested only in the form of gastritis, but in many cases they are entirely lacking.

From the irritation which the drug excites upon the mucous membrane of the cheeks, when long used, there may result, as Guipon<sup>2</sup> once observed, a stomatitis without salivation. In this case, the gums were of a dark-red color and swollen, and showed a violet border along their edges. The incisor teeth were of a slate color, and the buccal mucous membrane exceedingly sensitive, particularly to heat. More recently this affection has also been observed by Magitot,<sup>3</sup> and described as "gingivite argen-

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<sup>1</sup> Gamberini, Jour. de Médecine, Décembre, 1860.

<sup>2</sup> Guipon, Bullet. de Thérapeutique, 1866, vol. 71, p. 86.

<sup>3</sup> Magitot, Gazette des Hôpitaux, 1879, p. 165.

tique." He calls attention to the fact that Charcot saw a papular eruption appear upon the skin after the long-continued internal use of nitrate of silver, and states that both affections are to be regarded as local irritative effects produced by silver.

After the occurrence of arguria, the individual organs manifest the following changes:

Neumann,<sup>1</sup> on examining the skin, found the silver most abundant in the papillary layer. A few granules were also found in the other layers of the skin, most plentiful on the external wall of the hair-follicles, sebaceous glands, and sweat-tubes. The epithelial elements, the rete Malpighii, and the lining of the root-sheaths were free.

In the case of a man who had taken nitrate of silver in large doses for epilepsy, Frommann<sup>2</sup> found, post-mortem, an ulcer between the pyloric and cardiac orifices of the stomach. The duodenum and jejunum looked as if numerous little black granules had been scattered over them. These, most thickly crowded together along the tops of the folds, presented the appearance of a dark, striped pigmentation of the mucous membrane. In the duodenum they formed round spots, about one-half of an inch in diameter, darkest in the centre, and lighter in color around their edges. The intestinal villi contained groups of intensely black bodies, which were readily soluble in cyanide of potassium.

Rierner,<sup>3</sup> in the case of a man with *tabes dorsalis*, who in one year had taken five thousand six hundred and seventy-two pills containing 34.032 grams (3 viiiiss.) of nitrate of silver, found the surface of the kidneys gray, with numerous dark spots corresponding to the Malpighian bodies, and the mucous membrane of the pelvis grayish-blue in spots.

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<sup>1</sup> Neumann, Sitzungsberichte d. Gesellschaft Wiener Aerzte, 1 März, 1878.

<sup>2</sup> Frommann, Virchow's Archiv, Bd. xvii.

<sup>3</sup> Rierner, Archiv d. Heilkunde, 1876, xvi., p. 296 u. 385.

Virchow (l. c.) described the changes in the parenchyma of the kidneys produced by arguria, as he found them in a preparation in the collection of the Berlin Pathological Institute. In this, there is seen in the Malpighian bodies, where the transudation of fluid occurs, a blackish-blue discoloration of the walls of the vessels, limited to this point, and in a lesser degree to the connective tissue between the straight tubes. Therefore, in the whole kidney, besides those parts from which elimination occurs, only those are affected which correspond to the ultimate capillary distribution in the pyramidal substance.

In addition to the parts of the body already mentioned, silver has been found by Riemer and others in many other organs, such as the membranes of the brain, the liver, mesentery, walls of the vessels, the heart, etc.

Opinions differ as to the manner of absorption and deposition of the metal. Riemer believes that the pigment is taken up as such, *i. e.*, in the form of reduced silver, into the intestinal canal, is here stored up, and soon carried further through the lymphatic glands, being partially deposited on the way, the greater part being carried into the current of the blood. Thence it passes through the walls of the vessels, being partly deposited in them, the remainder becoming permanently fixed in certain portions of the tissues. Riemer, therefore, believes that the cause of arguria is dependent upon purely physical laws, as in the case of anthracosis pulmonum, and tattooing of the skin, in which opinion he is supported by the recent investigations of Huet,<sup>1</sup> who found that the particles of silver reached the tissues by a sort of diapedesis. Frommann, Delioux, and others, on the contrary, believe that silver salts can be taken up in the intestinal canal only in a state of solution, and they, therefore, claim that arguria occurs

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<sup>1</sup> Huet, Journal de l'Anatomie, 1873, p. 108.

in obedience to chemical laws, by precipitation at the affected points.

In the differential diagnosis between arguria and Addison's disease, the following points are to be considered, according to Gamberini. In the latter, the color varies between bronze and black, while in the former the skin is slaty-gray, with a reddish tinge. When the skin is washed with a solution of iodine, an evident change in color is produced, which is not the case in Addison's disease.

The treatment of arguria may be directed either to the gastric symptoms or to the discoloration of the skin. As regards the former, the existing evidences of intestinal irritation should be treated symptomatically. In order to produce a clearing up of the color of the skin, it is advisable, after the successful process of Gamberini, to try the internal administration of the iodide of sodium or potassium, and the long-continued use of warm baths. As regards prophylaxis, care must be taken that the silver is not used longer than three months, and to the extent of at most fifteen grams ( $\frac{3}{4}$  ss.)

#### PLUMBI ACETAS.

In view of the recognized poisonous nature of the acetate, as well as of most of the other preparations of lead, and the extensive internal and external employment of the agent in relatively large doses, it is remarkable that injurious incidental effects are not more frequently seen from its use than is really the case. Attention must, nevertheless, be directed to the fact that, in the cases of saturnism which arise in consequence of the technical use of lead or its introduction with the food, the consumption of the metal has usually been going on for a relatively much longer time than is the case with even the most prolonged use of the drug for therapeutic purposes, and that the majority of the functional disturbances in the lead disease



are produced by the extremely gradual deposition of minute quantities of the metal in the organs and its subsequent cumulative action. That there are exceptions to this mode of origin of lead poisoning is proved by the fact, particularly insisted upon by Romberg,<sup>1</sup> that certain persons, who are for a long time in contact with preparations of lead, nevertheless remain healthy, while others quickly suffer from its effects.

A few cases have been collected by Wibmer,<sup>2</sup> in which hurtful incidental effects followed the use of medicinal doses of the acetate of lead, probably owing to individual causes, such as diminished elimination of the lead by the intestines, the kidneys, etc. Baker<sup>3</sup> observed in a man who, to cure a hæmaturia, took for four days, morning and evening, 0.06 gram (gr. i.) of the acetate of lead, loss of appetite, pain in the stomach, constipation, and paralysis of one hand, lasting three weeks. In another case, after the use for three days of 0.24 gram (gr. iv.) daily, there occurred attacks of colic extending over several months. Tanquerel des Planches,<sup>4</sup> who was the first to study and carefully describe the action of lead, warns against the too extensive internal use of its preparations, on the ground that it readily produces unpleasant symptoms.

The external application of lead, in the form of solutions and ointments, is also said to be sometimes followed by unpleasant results. Those cases in which a discoloration of the skin of longer or shorter duration is caused by lead, are here first to be mentioned. Foucaud de l'Espagne<sup>5</sup> reports the case of a lady who, on the order of a physician,

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<sup>1</sup> Romberg: *Lehrbuch der Nervenkrankheiten*, i., p. 167.

<sup>2</sup> Wibmer, l. c., Bd. iv., p. 23.

<sup>3</sup> Baker, *London Medical Transactions*, i. and ii.

<sup>4</sup> Tanquerel des Planches: *Traité des maladies de plomb*, übers. von Frankenberg, ii., p. 343.

<sup>5</sup> Foucaud de l'Espagne, *Gazette des Hôpitaux*, 1863, No. 153, p. 611.



used a solution of the acetate of lead as an astringent eye-wash. In consequence of the simultaneous use of sulphur baths for rheumatism, on the order of another physician, a black discoloration of the edges of the eyelids ensued, which spread over the cheek-bones and was only removed after six days by washing the parts with infusions of aromatic herbs. Bérenger-Ferand<sup>1</sup> reports a similar observation. In this case, in spite of the use of various acid, alkaline, and alcoholic lotions and cosmetics, the black color persisted for thirty months.

The application of solutions of lead upon mucous membranes and the surfaces of wounds seems in very rare cases to produce poisonous effects. Such a case was observed by Tanquerel des Planches after the application of lead-water compresses to the eye.

Percival,<sup>2</sup> after the frequent application of the acetate of lead as a lotion to a contused shoulder, witnessed the appearance of gastric pains, which ceased with the discontinuance of the remedy and reappeared when it was again used. The washing of a large ulcer of the leg with lead-water, and the application of lead-plaster was followed four days later by attacks of colic and paralysis of the extremities, which soon passed off after the discontinuance of the drug. In another case, observed by Werdermann, after the application of lead-water upon an ulcer, there appeared a sweetish styptic taste in the mouth and stiffness of the neck. In this case also, the symptoms ceased and reappeared in accordance with the abandonment or renewed use of the drug.

From a physiological stand-point, there are no reasons for doubting the possibility of the occurrence of such effects of lead. Since it has been definitely proved that under certain circumstances an absorption of lead into the

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<sup>1</sup> Bérenger-Férand, *Gazette des Hôp.*, 1864, p. 62.

<sup>2</sup> Percival, on the Poison of Lead, London, 1774, in Wibmer, Bd. vi., p. 237.

system may take place even through the normal skin, the penetration of lead, particularly the caustic preparations which form precipitates with albumen, is comprehensible. Of course, only small quantities can be absorbed in this manner, nevertheless so much may be taken up, that after a few applications of the drug it may be demonstrated in the urine. The reason why injurious incidental effects so seldom follow this method of using the drug is unknown. Similar individual conditions, however, prevail with the majority of drugs, and are not dependent upon the manner of absorption.

#### ZINCI OXIDUM.

The oxide of zinc, as well as all other zinc combinations (except the sulphate) which, during the last few decades, have been much employed in the treatment of affections of the central nervous system, such as epilepsy, eclampsia, and chorea, produce, not infrequently, like other metallic salts, undesirable incidental effects, pertaining principally to the digestive tract. The doses after which they may appear range between as low as 0.2 and 0.3 gram (gr. iv.-v.). In many persons, there then occur nausea and a feeling of oppression in the epigastrium, differing in degree with the individuality of the person, and the amount of food in the stomach. For the irritating effect upon the gastric mucous membrane becomes more intense in proportion as the zinc salts have the opportunity, either directly or after their solution in the stomach, to form an albuminate by acting upon the mucous membrane. If there be sufficient food in the stomach to transform all the zinc into an albuminate, the irritating quality of the metal is almost entirely neutralized, since the albuminate goes through the regular digestive process, and is then taken up directly into the vascular channels.

In any event, the long-continued use of small doses of zinc salts should be avoided, since even with the greatest

care they may produce injurious effects upon different functions. Thus Werneck<sup>1</sup> observed in his own case, after taking repeated 0.24 gram (gr. iv.) doses of the oxide of zinc, oppression in the stomach, eructations, a slight fullness of the head, later dizziness and a sense of physical depression, and after the fourth dose intense thirst, pain in the stomach, slight vomiting, and a feeling of tension in the limbs. If the zinc salt reaches the intestines and is able to irritate the mucous membrane, diarrhœa is also associated with these symptoms. Similar effects have been observed by other authors, even after small doses taken at long intervals. It should also be stated that, according to Pereira, a zinc dyscrasia, analogous to chronic lead poisoning, may be produced by frequent use of medicinal doses of the agent, characterized by obstinate constipation, emaciation, and anæmia.

From a prophylactic stand-point, the symptoms detailed above may be easily prevented, if the zinc salt is administered in a soluble form, *e. g.*, as the lactate, and upon a full stomach. If, however, the incidental effects have appeared, milk and fluid albumen may be given, in order that they may combine with any zinc which may be present in the stomach. Every effort must also be made to cause its speedy elimination from the body, by the administration of laxatives and diuretics.

#### CADMII SULPHAS.

The sulphate of cadmium was employed internally by Grimaud<sup>2</sup> in the treatment of syphilis, chronic rheumatism, etc. It produces, in a still higher degree than the zinc salts, irritation of the stomach and intestines, which is, however, of a transitory nature. Burdach saw, after 0.06

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<sup>1</sup> Werneck, *Medic. chirurg. Zeitung*, 1831, iii., p. 317; ref. in Wibmer, l. c., Bd. v., p. 469.

<sup>2</sup> Grimaud, *Gazette médicale de Paris*, 1851.

gram (gr. i.), salivation, colic, and frequent stools with tenesmus.

An ointment of the sulphate of cadmium, according to Grimaud, produces pustules similar to those caused by an ointment of tartar emetic.

#### BARI CHLORIDUM.

The chloride of barium, which on the recommendation of Hufeland<sup>1</sup> was formerly employed as a specific in different forms of scrofula, sometimes causes in certain individuals, in quantities less than the maximum, 0.12 (gr. ij.) at a dose, 1.5 gram (gr. xxij.) daily, functional changes in different organs. According to the experience of Lisfranc,<sup>2</sup> the medicinal action of this drug is very variable, and much larger doses are borne in warm climates than in colder regions.

The disturbances to be noticed on the part of the stomach and intestines are nausea and even vomiting, anorexia, colicky pains, oppression in the epigastrium and diarrhœa. Catarrhal irritation of the conjunctiva, the nasal and respiratory mucous membranes (that of the last two probably extending from the pharynx) have been a few times observed after the use of baryta.

After the long-continued use of medicinal doses, the symptoms detailed may, as Hufeland also observed, increase to an excessive degree, even to the production of well-marked gastro-enteritis, and with this there may be associated symptoms affecting the central nervous system, such as giddiness, great anxiety, swooning, muscular weakness, trembling, and even convulsions. Kohl,<sup>3</sup> in a case in which chloride of barium was employed for twenty-four

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<sup>1</sup> Hufeland: Ueber die Natur, Kenntniss und Heilart der Scrofelkrankheit, Berlin, 1819.

<sup>2</sup> Lisfranc, by Bernatzik, Encyclopädie der ges. Heilkunde, 1880, Bd. ii, p. 15.

<sup>3</sup> Kohl, in Husemann, Toxicologie, p. 945.

days, observed salivation, swelling of the salivary glands, a bad odor from the mouth, and falling out of the teeth.

It is not improbable that this intensification of the symptoms produced by the long-continued use of baryta is due to a cumulative action of the drug, in consequence of its slow elimination with the urine and fæces. This hypothesis finds support in the fact that, as has been proven, the chloride of barium is transformed in the body into the sulphate, and this, an almost insoluble substance, is deposited at the point of its origin, and is afterwards gradually cast out of the system. In this way it is possible for a more intense action of the drug to occur, and one which lasts long after its use has been suspended.

In this manner also, an observation of Schwilgué<sup>1</sup> is explained. He found that when he gave small doses of baryta, the symptoms of irritation of different organs were intensified after the drug was stopped, and lasted at least seven weeks longer.

The treatment of the symptoms detailed consists, in the first place, in the suspension of the remedy. The gastric disturbances require symptomatic remedies for the relief of the inflammation. Diuretics are advisable to cause a more rapid elimination of the drug. The use of a direct antidote, such as the sulphate of sodium or magnesium, is indicated only in very bad cases.

#### ACIDUM TANNICUM.

Individual susceptibility to the action of tannic acid varies greatly in different persons. Tully, who took daily for a week 0.6 gram (gr. x.) of tannin, experienced nothing more than slight nausea and loss of appetite, while Hennig,<sup>2</sup> after even 0.2 gram (gr. iij.), experienced in his own case pain in the stomach and intestines, a coated

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<sup>1</sup> Schwilgué: *Matière médicale*, T. i., p. 409. \*

<sup>2</sup> Hennig, *Archiv f. physiol. Heilkunde*, Bd. xii., 1853.



tongue, eructations, thirst, tenesmus, and an increase of an habitual hemorrhoidal congestion.

After a large dose of tannin, taken for diarrhœa, Roller<sup>1</sup> observed pains in the stomach and abdomen, obstinate vomiting and constipation, lasting fourteen days, besides slight febrile movement. After the constipation was relieved, blood and pus were passed with the fæces. This was probably due to a cauterization of the gastric and intestinal mucous membranes by small particles of tannin.

In order to avoid such unpleasant effects and to still be able to take tannin for a long time, L. Lewin<sup>2</sup> recommends the administration of the albuminate of tannin, or of tannin in an alkaline solution. The former is easily prepared by dissolving the desired quantity of tannin in a little water, precipitating it by a solution of albumen, and adding albumen in excess to the albuminate of tannin thus formed until it is dissolved. For a solution of 2 grams (gr. xxx.) of tannin in 100 grams (℥ iij.) of water, the white of one egg dissolved in 100 ccm. (℥ iij.) of water and filtered, is sufficient. Tannin in an alkaline solution may be obtained by adding carbonate of sodium to the desired solution of tannin until the reaction is slightly alkaline, or by adding albumen to it, and again dissolving the tannate of albumen by the addition of carbonate of sodium.

#### ERGOTINUM.

Both the *extractum secalis cornuti* of Wiggers and that of Bonjean produce now and then in medicinal doses (0.2 to 0.4 gram) (gr. iij. to vij.) a disagreeable taste in the mouth, tickling in the throat, increased flow of saliva, nausea, burning in the stomach, pains in the abdomen, eructation,

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<sup>1</sup> Roller, Wiener med. Wochenschr., 1865, 97.

<sup>2</sup> L. Lewin: Untersuchungen über Wirkung und Verhalten des Tannins im Thierkörper. Virchow's Archiv, Bd. 81, 1880.



vomiting, and diarrhœa. With some of these symptoms there may be associated fulness in the head, headache or chilly sensations, giddiness, dilatation of the pupils, and general lassitude, unsteadiness of gait, and irregularity of the pulse. Aside from the individuality of the patient, the differences in the mode of action of the drug are probably to be attributed to variations in its chemical composition.

A number of undesirable incidental effects have also been observed after the subcutaneous injection of ergotin, first employed by Von Langenbeck<sup>1</sup> (Extr. secal. corn. Bonjean, 2.5 (gr. xxxviii.); spts. vini, glycerini, āā 7.5 (gr. cxiii.). This author, after the injection of 0.3 gram (gr. v.), noticed the occurrence of specks before the eyes, and pain in the shoulder, and Eulenberg<sup>2</sup> saw dizziness and vomiting.

More threatening were the general symptoms which appeared in a case reported by Rezek,<sup>3</sup> after the injection of 0.04 gram (gr.  $\frac{2}{3}$ ) of ergotin. Five minutes afterwards, the patient made a few convulsive movements with the whole body, the pupils became dilated, the eyeballs rolled, unconsciousness occurred, the skin became cool, and the pulse ceased. Cold douches and the internal administration of ether dissipated these symptoms.

Hildebrandt<sup>4</sup> witnessed milder symptoms. In the case of a lady, after six injections, there appeared dizziness, uncertainty of motion, spasmodic contractions of the flexors of the upper and lower extremities, nausea, and a sense of constriction of the chest. As soon as the use of the drug was discontinued, these phenomena disappeared, to return when it was again employed.

More common than these general manifestations are the

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<sup>1</sup> V. Langenbeck, Berl. klin. Wochenschr., 1869, p. 117.

<sup>2</sup> Eulenberg: Die hypodermat. Injection der Arzneimittel, Berl., 1875, p. 240.

<sup>3</sup> Rezek, ref. by Eulenberg, l. c., p. 244.

<sup>4</sup> Hildebrandt, Berl. klin. Wochenschr., 1872, p. 298.

more or less intense local symptoms of reaction. After nearly every injection, a painful, nodular infiltration is formed at the point of puncture, and in its immediate neighborhood, which does not result in suppuration. Hildebrandt, who used injections of ergotin in the treatment of fibro-myomata of the uterus, believed that the pain caused by the injection of the fluid recommended by Von Langenbeck was due to the alcohol which it contains. He, therefore, used a solution of Extr. sec. corn. aq., 3.0 (gr. xlv.) in glycerine and water, āā 7.5 (gr. cxiii.), and found that it caused less pain, but there remained, after the injection, persistent, somewhat sensitive, nodules.

Bengelsdorff,<sup>1</sup> after the injection of ergotin according to Hildebrandt's formula (the ergotin in it is not entirely dissolved, but a large part suspended), often saw decided pain and not infrequently a true phlegmonous, not suppurative, inflammation spring up more or less extensively around the point of injection. At the same time there was usually formed a hard nodular swelling, corresponding in size to the quantity of fluid injected, which often remained eight days or longer. Carrying the canula deep down into the tissues and rubbing the skin did not hinder the formation of the nodules.

#### FOLIA SALVIE.

The favorite popular remedy, salvia leaves, which are occasionally administered internally in the form of an infusion as an astringent, may, under certain circumstances, produce disagreeable effects, as is shown by an experiment of Pidoux upon himself, who, after taking a cold infusion of the drug, experienced profuse sweating, lasting several hours; a bitter taste, and a feeling of dryness in the mouth and throat, obstinate constipation, and increased frequency

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<sup>1</sup> Bengelsdorff, Berl. klin. Wochenschr, 1874, p. 21.

of pulse. These symptoms represent the combined effects of the tannin and the ethereal oil contained in the plant.

### PIX LIQUIDA.

Tar, which was formerly much used internally in the form of tar-water, in the treatment of skin diseases and bronchial affections, is now usually employed only externally, either pure, as an embrocation for the treatment of eczema, or as an inhalation in the form of tar-water. In either form it is capable of producing undesirable deleterious effects, if large quantities of the more active substances which it contains are absorbed.

These effects may be general or local. The general manifestations produced by the absorption of small quantities, are nausea and inclination to vomit, and, after larger quantities, headache, a feeling of giddiness, vomiting or diarrhœa, associated with abdominal pains.

The local symptoms are due to an inflammatory irritation of the normal, and, in a still greater degree, of the morbidly altered skin, probably caused by the carbolic acid and creasote, or the empyreumatic substances contained in the tar. In consequence of this local irritation, there is produced, according to Hebra,<sup>1</sup> an acne which appears in the form of hard red nodules, and lasts as long as the influence of the tar is present. A tar-acne, once developed, undergoes involution very slowly, requiring on an average a period of two to four weeks for its disappearance, which occurs, however, without leaving scars or pigmented spots behind. Wilkinson's sulphur and tar ointment, modified by Hebra (Sulphur. præc., Pic. liquid., āā 180 (ȝ vss.), Cretæ, 120 (ȝ iv.), Sapon. vulg., Adipis, āā 500.0 (O.i.), used for the treatment of scabies, also causes eczema, either by being brought in contact with healthy

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<sup>1</sup> Hebra: *Lehrbuch der Hautkrankheiten*, i., p. 594.

parts, or in consequence of the great sensitiveness to ointments shown by many persons.

The urine passed after the application of tar often shows changes which are probably due to the carbolic acid in the tar, and which point to its absorption into the blood. Petters<sup>1</sup> found the urine of an intensely blackish-brown color, with the characteristic odor of tar. Upon distilling it with sulphuric acid, he obtained in the distillate carbolic acid and heavy dark-brown oil-drops, similar to creasote. For the sake of analogy, it should be stated that the dark urine which is occasionally passed after treatment with carbolic acid, contains hydroquinone, an oxidation-product of carbolic acid.

#### OLEUM JUNIPERI EMPYREUMATICUM, OR OLEUM CADINI.

The oil of cade, obtained by dry distillation from *Juniperus oxycedrus*, not infrequently excites inflammatory action, when applied to the skin. Kleinhaus,<sup>2</sup> who applied the undiluted oil, as is usually done, directly upon the surfaces affected with acute, chronic, or impetiginous eczema, noticed that even when the skin was but moderately inflamed, a tolerably intense redness and swelling, with acute pain, was developed in consequence of the action of the oil, and that soon after the hair-follicles projected above the skin in the form of nodules of the size of a hemp-seed—an affection which was seen to be identical with tar-acne.

Bazin observed in patients who used inunctions of the oil of cade in the treatment of psoriasis, an eruption of isolated or grouped papules, but slightly confluent, hard, of considerable size, surrounded by a halo, most plentiful on those parts covered with a well-developed growth of hair.

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<sup>1</sup> Petters, *Prager Vierteljahrschr.*, 1855, Jahrg. xii., Bd. 3.

<sup>2</sup> Kleinhaus, *Allgem. med. Centralzeit.*, 1863, No. 24, p. 185.

They were seated upon broad nodular bases, and ended in a sharp point, or sometimes a vesicle. A little black point, due to the presence of a hair, was always found at the summit. These nodules almost never suppurate, and even when scratched, only at their apices. The hair-follicles are the seat of the affection. Bazin designated it *cadecycosis* (*sycosis cadique*).

In many cases, according to Kleinhaus, the swelling and inflammation extend from the original point of application over a large extent of surface, and may then present the picture of a dermatitis, complicated by erysipelas; in fact, even the lymphatic vessels and, through sympathy, the lymphatic glands, may participate in the inflammatory process.

In the milder form of the affection first described, hydropathic applications, with soothing ointments and the discontinuance of the drug, suffice to cause the disappearance of the disease.

To diminish the pain in the wide-spread dermatitic form, it is advisable to employ warm baths, in which the patient should remain for from one-half an hour to an hour, and to give small doses of opium internally.

An incidental effect of less importance is the brown color of the skin produced by oil of cade, which is very difficult to remove. In order to avoid this inconvenience, the oil may be used in the form of a soap, as Kleinhaus did, according to this formula:  $\mathcal{R}$ . Butyr. Cacao, 12.0 (3 iij.); Ol. Cadini, 9.0 (3 ij. gr. xv.); Ol. Lini, Liq. Ammonii caust.,  $\overline{aa}$  4.0 (3 i.). Of this 5 to 10 grams (3 i. to 3 ij.) are rubbed in, according to the extent of surface affected. This soap can be easily washed off with water.

#### ACIDA.

The dilute inorganic acids, such as sulphuric, hydrochloric, phosphoric, and nitric, and the fruit acids, as citric,

tartaric, etc., cause not infrequently, when taken for a long period, disturbances of digestion. The appetite diminishes, the tongue becomes coated, the teeth ache, and pains in the stomach and eructations occur, and sometimes salivation and diarrhœa.

After the long-continued use of dilute nitric acid, according to Mitscherlich,<sup>1</sup> the gums and the tongue often become ulcerated; the former bleed readily and the teeth are loosened—symptoms which must be regarded as purely local effects.

#### ACIDUM CARBOLICUM.

The fact that in some persons disturbances of the general nervous system sometimes follow the internal use of carbolic acid in medicinal doses has been recognized since the first employment of the remedy. Declat<sup>2</sup> observed slight headache after its use, lasting from five to fifteen minutes, spreading over the whole head, and returning every time the drug was taken, most intense in some persons in the frontal region, in others in the occipital. After the administration of the acid in the form of pills, Neumann observed heaviness and fulness of the head, weakness of the legs, dizziness, the appearance of circles before the eyes, horripilation, and profuse sweating.

Only during the past few years has the attention of physicians been directed to the exceedingly injurious, even fatal, consequences which may, under certain circumstances, follow the external employment of carbolic acid in the treatment of wounds. The majority of observers believe that in the production of this result the individuality of the patient is a factor, the nature and power of which is unknown to us, but which exerts an immense, if not an exclusive influence in bringing about such injurious incidental effects.

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<sup>1</sup> Mitscherlich: *Lehrbuch d. Arzneimittellehre*, Bd. iii., p. 81.

<sup>2</sup> Declat: *Traité de l'Acide phénique*. Paris, 1854.



Thus Busch<sup>1</sup> regards carbolic acid as one of the drugs which, indeed, act favorably in medicinal doses, but to which certain individuals, for reasons as yet unknown, are so sensitive that quantities harmless to innumerable other persons act poisonously upon them.

Carbolic acid may gain entrance into the body after any method of application. The acid can be detected in the tissues, the blood, and the secretions and excretions, as well after its application to the healthy skin as to the surfaces of wounds and mucous membranes. In each of these methods of application, there may be produced that condition described under the name of "carbolism," by which we understand an abnormal action of carbolic acid produced by one or more medicinal doses.

It was formerly believed that the most certain criterion of the existence of carbolism was the emission of urine already brown or greenish when passed, or, if of a lighter color then, becoming blackish-brown or deep-brown after exposure to the air. Bill believed that the carbolic acid was transformed into quinone in the body, and that this substance gave the urine its black color. Quite recently Baumann and Preusse<sup>2</sup> have given the true explanation of this discoloration of the urine. They proved by analysis of such urine that, in addition to colored products, it contained hydroquinone in the form of hydroquinone-sulphuric acid. According to this, a large part of the carbolic acid introduced into the body is transformed into hydroquinone by oxidation. One portion of this is further oxidized in the system into indefinite colored products which pass into and color the urine, while the larger part appears in this fluid as hydroquinone-sulphuric acid. The dark color seen in many specimens of urine containing carbolic acid after standing, is due to the fact that

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<sup>1</sup> Busch, Berl. klin. Wochenschr., 1880, p. 304.

<sup>2</sup> Baumann and Preusse, Archiv f. Anatomie u. Physiol., 1879, p. 245.

the eliminated hydroquinone-sulphuric acid is split up, and the hydroquinone thus set free, is oxidized under the influence of the air, to form colored compounds. The more alkaline the urine, the more rapidly this takes place.

Careful observations have determined that this carbolic-acid urine does not always appear as a pathognomonic symptom of the occurrence of noxious incidental effects, but that, in a number of cases, it is much rather a series of but little characteristic, although dangerous, symptoms which make up the picture of carbolism, and may lead to a fatal issue. Küster,<sup>1</sup> who called attention to the poisonous qualities of carbolic acid particularly in the antiseptic treatment of wounds, maintained that the reason why so few cases of death are recorded in consequence of the employment of carbolic acid is, that the majority of them, on account of the uncertainty of the symptomatology, are concealed under the names of shock, collapse, and similar terms. Of five such cases which he observed, four had a fatal termination. As predisposing to the occurrence of a deleterious action of carbolic acid, he mentions bodily weakness and pre-existing diseases. V. Langenbeck<sup>2</sup> saw a case of severe carbolic-acid poisoning in the treatment with carbolic paste, of abscesses in a boy, and two others, ending fatally, after insignificant operations followed by the application of the dry dressing. Rose<sup>3</sup> also reported a case in which, after the application of carbolized cotton which smelt very strong of carbolic acid and was still moist, gangrene occurred in a finger which was the seat of a wound in full process of healing.

A striking illustration of the symptomatology of carbolism is furnished by a well-observed case of Busch (l. c.). A boy, upon whom an operation for the opening of an

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<sup>1</sup> Küster, Berl. klin. Wochenschr., No. 48.

<sup>2</sup> Langenbeck, eod. loco, 1878, No. 48.

<sup>3</sup> Rose, Verhandlungen d. Gesellschaft d. Aerzte in Zurich, 19 Dec., 1874.

abscess under the trochanter had been performed, and who was exposed to a two-per-cent spray of carbolic acid during the few minutes necessary for the operation, and afterwards to the action of carbolized gauze, was seized on the same day with vomiting, which was attributed to the chloroform which had been used. After the dressing was opened the next morning under the carbolic spray, an inclination to renewed vomiting appeared, and in the evening carbolic urine was passed, and later symptoms of collapse showed themselves, the pulse becoming small and frequent, and the temperature falling to 35.5° C. (96.5° F.). The frequent vomiting made it impossible to introduce anything into the stomach, and in spite of the subcutaneous and external employment of analeptics, the patient died fifty hours after the operation.

As an instance of a local organic affection, it may be stated that Lücke<sup>1</sup> observed a nephritis due to the action of carbolic acid, which disappeared when the use of the drug was stopped. E. Wagner<sup>2</sup> studied the changes in the kidneys with greater care. Carbolic acid was applied in a case of gangrene of the leg. The next day, carbolic acid urine was passed, containing casts of medium width, the majority hyaline, and a few fatty, some studded with red blood-corpuscles or renal epithelium. After death, microscopic examination showed that the uriniferous tubules were dilated, their epithelia large and very fatty, projecting far into their cavities, which contained numerous masses of protoplasm and jagged shining bodies.

In our opinion, not enough importance has been attributed to the action of the spray in the discussion of the subject of the absorption of carbolic acid during the antiseptic treatment. Olshausen<sup>3</sup> believes that the skin is

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<sup>1</sup> Lücke, Berl. klin. Wochenschr., 1878, p. 248.

<sup>2</sup> Wagner, Deutsches Archiv f. klin. Medicin, 1880, p. 529

<sup>3</sup> Olshausen, Berl. klin. Wochenschr., 1878, p. 248.

rendered much more capable of absorbing the agent under the influence of the first dressing, and Langenbuch<sup>1</sup> maintains that absorption by this organ is underestimated in comparison with that from wounds, and believes that perhaps more is taken up by the normal skin than by the surfaces of wounds, during the cleansing process. As favoring absorption, he regards the soaping, shaving, and scraping of the skin, by which the sweat-glands are opened, as well as the literal bathing of the skin by the spray.

The latter, however, operates in still another manner. It has been proved by the investigations of Röhrig<sup>2</sup> that finely pulverized watery solutions of substances are taken up by the skin, while they are not absorbed when simply laid upon it. The experiments bearing upon this point, which were made with all possible precautions, showed that when watery solutions of the iodide or ferrocyanide of potassium, *e. g.*, were applied to the skin in a finely divided condition, one or the other of these drugs appeared in the urine. Animals could also be stupefied or brought into a paralytic condition by solutions of morphia or woorara applied in the same manner. This proves that the act of atomizing introduces substances into the body much more easily and in larger quantities than simple contact. Therefore, the belief is fully justified that a very large portion of the carbolic acid employed in the spray is absorbed by the skin or its sweat glands. It also becomes clear that carbolic-acid poisoning may easily occur under these circumstances in the cases of children, who naturally possess a much more limited power of resistance, since the surface of the skin acted upon by the spray is much larger in proportion to the entire surface of the body than in adults, and therefore, *cæteris paribus*, much more carbolic acid is taken into the system. Never-

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<sup>1</sup> Langenbuch, *op. cit.*, 1878, p. 414.

<sup>2</sup> Röhrig: *Physiologie der Haut*, 1878, p. 116.

theless, the prejudicial influence of soaping, brushing, and shaving (manipulations against which Lister has also spoken) in facilitating the occurrence of hurtful incidental effects, must not be underestimated.

After what has been said, it will be readily understood that the introduction of carbolic acid into cavities lined with mucous membrane may also lead to carbolic-acid poisoning. The application of enemata containing carbolic acid, and the irrigation of the uterus and vagina with this drug, should be considered in this connection. Thus Prätorius,<sup>1</sup> in the case of a woman in whom an irrigation of the rectum with a weak carbolic acid solution—one-quarter litre ( $\frac{2}{3}$  viij.) of a one-per-cent solution to one-third litre ( $\frac{2}{3}$  x.) of warm water—was employed, noticed, after a third of this solution had been used, ringing in the ears, dizziness, weakness, and fainting fits. Kottmeyer<sup>2</sup> describes exactly analogous phenomena after the use, per enema, of a half-per-cent solution of carbolic acid, in the case of a boy suffering from oxyurides.

Olshausen (l. c.) observed severe symptoms of poisoning after washing out the uterus, and Löhlein<sup>3</sup> saw evidences of carbolism appear two days after carbolic-acid injections into the vagina and uterus of lying-in-women. It must finally be mentioned that Edwards, after the introduction into the vagina of tampons of cotton impregnated with carbolic acid, saw singultus, nausea, chilliness, and anasarca, with diminution or suppression of urine, delirium, and, finally, death. He attributes these phenomena to an acute nephritis, with uræmia, produced by carbolic acid.

The treatment of carbolism should vary with the manner in which the acid was taken into the body. A directly antidotal therapeutic proceeding is generally without re-

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<sup>1</sup> Prätorius, Berl. klin. Wochenschr., 1879, p. 214.

<sup>2</sup> Kottmeyer, eod. loc., 1879, p. 501.

<sup>3</sup> Löhlein, eod. loc., 1878, p. 25.

<sup>4</sup> Edwards, Virchow-Hirsch's Jahresber., 1869, 1, p. 349.

sult. Husemann and Ummethun recommend the saccharate of lime as an antidote, on the ground that lime forms with phenol an insoluble compound, but slightly poisonous. The sulphate of sodium is also said to act as antidote, by combining with phenol, to form the harmless phenol-sulphuric acid.

If the drug was introduced by enema, it would be well to thoroughly wash out the intestine, if only a short time have elapsed between the injection and the arrival of the physician. In the case of carbolism as ordinarily seen, arising from absorption from the skin or from wounds, a rapid symptomatic treatment of the general symptoms is indicated. The internal or subcutaneous use of stimulants, energetic irritation of the skin, sinapisms, frictions, and the faradic current, will aid in this object. For the vomiting, ice-pills and vegetable astringents should be administered.

#### ALTERATIVES.

##### HYDRARGYRUM.

Mercury occupies the first place among the remedies which, from their extensive therapeutical employment, very frequently produce symptoms which cause uneasiness to the physician, and much more to the patient. The affections produced by its external or internal employment are of manifold nature. They consist both of anatomical lesions of the skin and mucous membranes, and of purely functional disturbances of various organs without demonstrable changes, *e. g.*, of the salivary glands, and also of disturbances in the domain of the peripheral and central nervous systems. This condition has been described under the name of "hydrargyrosis," or "mercurialism."

In order to obviate the numerous external accidents, as well as the directly injurious incidental effects which frequently occur after the traditional methods of using mer-



cury, several new modes of administration have been recommended during the last few decennia, particularly for the treatment of syphilis. Inunctions of gray ointment, formerly employed in horrible doses—as much as 500 grams ( $\frac{3}{4}$  xvi.) daily—are well known to still frequently produce undesirable results, perhaps for the reason that, while in this manner too small a quantity of the drug is taken into the body to destroy the syphilitic poison in a short time, the mercury absorbed at long intervals, although small in amount, is sufficient to act injuriously when the necessary predisposition thereto is present.

The long-continued administration of calomel is also sometimes followed by unpleasant results, owing to the fact demonstrated by Radziejewski,<sup>1</sup> that when the drug remains long in the cæcum, it is transformed by contact with chloride of sodium or ammonium into corrosive sublimate, and thus may cause corrosion and ulceration.

For this reason, the treatment of syphilis with subcutaneous injections of the bichloride of mercury, introduced by G. Lewin,<sup>2</sup> in which almost all of the drug is carried into the circulation, is to be regarded as an important step forward, even although incidental effects are occasionally observed to follow the use of the drug in this manner also. Quite recently, two other combinations of mercury have been recommended for subcutaneous injection by Bamberger,<sup>3</sup> with a view to avoid the local irritation often produced by corrosive sublimate. One is a solution of the albuminate of mercury, prepared from 100 cubic cm. ( $\frac{3}{4}$  iij.) of a filtered solution of albumen (three to four parts of water to one part of albumen), sixty ccm. ( $\frac{3}{4}$  xv.) of a five-per-cent solution of corrosive sublimate, sixty ccm.

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<sup>1</sup> Radziejewski, *Archiv für Anatomie und Physiologie*, 1870, p. 22.

<sup>2</sup> G. Lewin: *Die Behandlung der Syphilis mit Subcutaner Sublimatinjection*, Berl., 1869.

<sup>3</sup> Bamberger, *Wiener med. Wochenschr.*, 1876, No. 11 and No. 44, p. 1074."

(3 xv.) of a twenty-per-cent solution of common salt, and eighty ccm. (5 iiss.) of distilled water. One ccm. (gtt. xv.) of this fluid, which becomes clear after filtration and standing for two days, contains 0.01 gram (gr.  $\frac{1}{6}$ ) of the bichloride in combination with albumen.

This solution produces no local irritative effect whatever. This author recommends still more strongly a solution of mercurial-peptone, prepared as follows: one gram (gr. xv.) of commercial meat-peptone is dissolved in fifty grams (5 iiss.) of water, and the solution filtered. To the filtrate, twenty ccm. (3 v.) of a five-per-cent solution of the bichloride of mercury is added, and also, in order to dissolve the resulting precipitate, fifteen to sixteen ccm. (5 ss.) of a twenty-per-cent solution of common salt. The whole quantity of liquid is diluted with water to 100 ccm. (5 iij.), and filtered, after standing for several days. Each ccm. of this solution then contains 0.01 gram (gr.  $\frac{1}{6}$ ) of mercury, in form of a peptone combination. The elimination of the mercury by the kidneys, when these fluids are injected, is said to be extremely rapid. In any event, great value should be attached to the method, since in this manner a cure is much more rapidly effected, and the organism is not long exposed to the action of mercury.

We commence the description of the incidental effects of mercury with the:

*Changes in the Skin.*—The affections of this organ, which show themselves in some persons in consequence of the use of mercury, appear in the shape of erythemata and eczemata (eczema mercuriale).

The latter was first observed by Benjamin Bell<sup>1</sup> and also by Pearson, while Alley<sup>2</sup> furnished the first exact descrip-

<sup>1</sup> Benjamin Bell: Treatise on Gonorrhœa violenta and Lues venerea, ii., p. 228.

<sup>2</sup> Alley: Observations on the Hydrargyria, or that vesicular disease arising from the exhibition of mercury. Dublin, 1804.

tion of this affection, which he called "hydrargyria." Hebra<sup>1</sup> and also Kussmaul<sup>2</sup> deny that it possesses any characteristic peculiarities as regards its course or symptoms, and therefore regard it as identical with ordinary eczema, while Bouchardet considers it a disease *sui generis*.

According to the statements of older observers, eczema mercuriale, which is usually seen only after the external employment of mercury, sometimes follows its internal administration also. Thus Alley (l. c.) saw it in an adult after taking 0.12 gram (gr. ij.), and in a girl after 0.18 gram gr. iij.) of calomel. Ascherson found it in a young man after 0.24 gram (gr. iv.). Fournier has recently reported a similar case, and Engelmann<sup>3</sup> has cited an instance in which, after the use of 0.45 gram (gr. vij.) of calomel in 0.15 gram (gr. iiss.) doses, there appeared, two hours after the last dose, an erythema on the head, attended with febrile movement, swelling of the face, etc. The disease spread in one night over the whole body, with intense burning and itching, and great weakness. Four days later, the fever diminished, and the skin began to desquamate on the face and breast, partly in large scales, as in the case of scarlatina. Appetite and strength returned very slowly. The affected person stated that he had frequently suffered in the same manner after taking mercury internally.

In opposition to this view, Hebra denies most positively the occurrence of this eruption from the internal use of any of the preparations of mercury. In any event, its appearance is extremely rare, and it seems that it can only take place under the influence of some individual predisposition.

On the other hand, this eczema not infrequently follows

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<sup>1</sup> Hebra: *Hautkrankheiten*, i., p. 452.

<sup>2</sup> Kussmaul: *Untersuch. über den constitutionellen Mercurialisums*. Würzburg, 1861.

<sup>3</sup> Engelmann, *Berl. klin. Wochenschr.*, 1879, p. 647.

the longer or shorter *external application* of mercury, most commonly the inunction of gray ointment. In some persons it shows itself after very small doses of mercury, and in many others it fails to appear even after the long-continued use of large doses. Alley found that twice as many men as women suffered from it, which is probably due to the fact that men require the use of gray ointment much more frequently than women.

Hebra defines mercurial eczema as a disease of the skin which appears in the form of red papules, vesicles, or small pustules in great number and closely aggregated. Alley distinguishes, according to its intensity and course, three forms of the eczema: 1. Hydrargyria mitis; 2. Hydrargyria febrilis; 3. Hydrargyria maligna. Such a division is, however, entirely arbitrary, all three forms of the eruption being essentially the same.

The exanthema sometimes appears after one, but usually after repeated inunction of gray salve, with intense itching and burning, usually on the internal surfaces of the thighs, the scrotum (or vulva), and in the groins, more rarely on the arms, back, and face. In many persons, during the whole course of the eruption, there are present febrile movement, headache, sleeplessness, and gastric disturbances. The affected portions of skin are covered with dark-red spots readily disappearing on pressure, varying in size, and soon running together over a large surface, upon which are seated vesicles of pin-head size, and very rarely large bullæ, with at first clear, later cloudy contents, which may burst or dry up. As a rule, after this eruption, which sometimes resembles measles and again scarlatina, has lasted for four or five days, the skin becomes paler and desquamation begins in large masses or small scales. Complete recovery usually takes place in from eight to fourteen days.

In many cases the disease is especially annoying to the

patient, owing to the fact that large portions, sometimes the whole, of the body are affected by the eruption; that high fever with angina of the fauces is present, and that from the irritating and bad-smelling contents of the numerous pustules, which burst or are scratched open, and which may also undergo relapses, painful excoriations, swelling of the skin deprived of epidermis, and the formation of crusts may occur.

In such bad cases of eczema repeated desquamation of the epidermis is sometimes observed, and occasionally, although rarely, falling out of the hair. This latter occurrence is especially worthy of notice, because in animals which have taken mercury for some time, it is the only evident effect of the drug upon the skin.

In addition to these affections of the skin, it is said that mercury may, in rare instances, after its external application, cause the formation of gangrenous ulcers, or even gangrene. We must, however, agree with Gwalter<sup>1</sup> in regarding the existence of such an effect of mercury as not proven.

Nothing positive is known as to the manner of occurrence of the mercurial eruption after inunctions of gray salve. Two possibilities are here to be considered, according to either of which it may be supposed that the absorption occurs. According to one theory, the preparation of mercury, applied by inunction, unfolds its action by being vaporized by the heat of the body, and thus gaining an entrance into the lungs and the system at large. From this point of view, the above-described affections must occur secondarily, after the circulation of the drug in the organism, and its transformation into corrosive sublimate or an oxide of mercury.

If, however, we adopt the other view, according to

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<sup>1</sup> Gwalter: Ein Fall von Quecksilbervergiftung. Inaug. Dissert., Zurich, 1877.



which the oleate of mercury, which is constantly being formed by rubbing the drug with fat, is absorbed as such by the skin, we must suppose that the eruption is due to the directly irritating effect of the mercury upon this organ. This irritation, if long continued, may lead to a hyperæmia of the dermal capillaries, swelling of the epidermis and sebaceous follicles, and consequently to exudation and the formation of papules and vesicles. The latter is probably the most common, if not the only mode of origin of the skin affection. This seems all the more probable, because the oleic combinations of mercury may exert a corrosive action, like the bichloride, and also because when mercurial preparations, even corrosive sublimate, are suddenly introduced into the circulation, *e. g.*, by subcutaneous injection, neither erythemata nor eczematata are ever observed. There, therefore, seems necessary for the production of the latter affections, a long-continued action of a soluble salt of mercury upon large portions of the skin, such as is furnished by repeated inunctions of gray salve, containing combinations of mercury with a fatty acid. This, however, does not preclude the possibility of the occurrence of skin changes from the internal use of mercury, which, in view of recent observations on this point, seems likely.

In opposition to the view held by the so-called anti-mercurialists, concerning the specific character of affections of the skin which follow the use of mercury, attention need only be called, without entering into subtle deductions, to the numerous eruptions mentioned in this work, produced by the most heterogeneous substances. These present a complete analogy among themselves, and the only specific element which they manifest is a direct or reflex action upon the skin.

The treatment of mercurial eczema consists in the immediate suspension of the drug, and the local application of soothing oils, salves, or vaseline.



A second incidental effect of the use of mercury, which occurs in about thirty or forty per cent of all cases, is *salivation* or *stomatitis*. Usually only twenty-four or forty-eight hours, in rarer cases two or three hours after the internal or external use of preparations of mercury in medicinal doses, there appears either alone or simultaneously with redness, swelling, softening, and sensitiveness of the gums, or before these symptoms, a sometimes quite excessive secretion of saliva, even as much as five kilos (eleven pounds) in twenty-four hours, which may last all night, and prevent the patient from sleeping. It persists usually for from three to ten days, or longer, and is attended with an offensive odor from the mouth and a subjective metallic taste. The saliva itself offers nothing especially characteristic. Its specific gravity may rise in the commencement of the salivation to 1.059, but later falls again. After some time it smells bad, has a strongly alkaline reaction, and irritates the soft parts over which it flows. The gums, the mucous membrane of the cheeks and palate, the tongue, the soft palate, and also the tonsils, experience changes varying in degree according to the individuality of the patient, the length of time during which the mercury was employed, and the amount of the drug used. The changes embrace all stages, from simple hyperæmia to the formation of ulcers and necrosis of tissue.

In the milder grades of mercurial stomatitis, the edges of the readily-bleeding gums are covered with a stinking yellowish, greasy mass. The teeth may even become loose. The ulcers, which are present in the severer forms, show a tendency to spread in depth and extent. They generally have smooth, jagged edges, and a base covered with a thin yellowish secretion. Not infrequently swelling of the lymphatic glands of the neck is also observed.

The subjective general disturbances which accompany these affections are exceedingly annoying, even in the milder forms. The constant flow of saliva causes sleeplessness, in

consequence of the necessity of either expectorating or swallowing it. To this is added pain, whenever articles of food come in contact with the inflamed or ulcerated parts. The swelling of the tongue, which frequently occurs, interferes with speech, and slight fever, which is often present, loss of appetite, headache, and bodily weakness, render the condition of the patient a very unpleasant one. After the affection has lasted for several days, if the use of the drug has been meanwhile suspended, the flow of saliva becomes less profuse, the changes in the mucous membrane of the mouth begin to disappear, and the ulcers which may be present, to heal, leaving star-like cicatrices behind. If more extensive destruction of tissue be present, many weeks and months elapse before complete restoration occurs.

The observation has been made that there are two factors which predispose to the occurrence of the affection of the mouth, and particularly the salivation. These are: 1, uncleanness of the mouth; and 2, a weak anæmic condition of the body, or previous severe diseases.

The affections considered above may also be produced by subcutaneous injections of mercury. This fact, combined with the circumstance that mercury may be found in the saliva, where it probably exists in an organic combination, proves among other things that the elimination of the metal occurs through the salivary glands, no matter what the manner of its use. In this way are explained the salivation and the tissue-changes in the mouth, since we must believe that, in the first instance, the irritating action of the eliminated mercury upon the tissues of the parotid or submaxillary gland, or their nerves, must cause, by a reflex action, the increased secretion of saliva, and that, further, the thus eliminated saliva, which contains mercury, if it act long enough, and contain a sufficient quantity of the drug, must produce inflammation or ero-

sion of those parts of the buccal cavity with which it comes in contact.

The treatment of a mercurial affection of the mouth must, in the first place, be prophylactic. For this purpose, patients must attend to cleanliness of the teeth, especially removing all products of decomposition contained in carious ones. Attention must also be paid to nutrition, in view of the predisposition shown by badly nourished individuals to the development of such affections. In prophylactic and curative therapeutics, the first place, after the discontinuance of mercury, is still occupied by the chlorate of potassium, first recommended by Herpin. This acts most safely and speedily upon the affections of the mouth. It should be prescribed in a two to three per cent solution as a gargle, and also internally to the extent of two to three grams (gr. xxx.-xlv.) daily. In cases of pure salivation, a solution of astringents (sol. Acid. Tannici, 1.0-3.0 : 150.0) (gr. xv.-xlv. :  $\frac{3}{4}$  iv.) renders good service when used for washing the mouth. Besides chlorate of potassium, alum in one to one and a half per cent solution is also used for the same purpose. Sigmund uses tar for painting the gums during treatment by inunction, both for the prevention of mercurial stomatitis, as well as for curing it when already present. Gums which bleed easily, may be pencilled to advantage with Tinct. Myrrhæ, or equal parts of Tinct. Myrrhæ and Tinct. Kino, or with Tinct. Rhatanæ. These last remedies should also be used for the cleansing of foul ulcers of the mouth, if it be not preferred to employ pure disinfectants, such as carbolic acid (0.5-1 : 150) (gr. viij.-xv. :  $\frac{3}{4}$  ivss.) or thymol (0.5 : 500) (gr. viij. : O. i.).

The incidental effects of mercury hitherto described are by far the most common, and occur as well after large and medium as after small doses. Although their duration is relatively short, they are included in the collection of symptoms designated as mercurialism. They only prove that the mercury has been absorbed, is circulating

through the body, and causing certain functional or anatomical changes at one of its points of entrance or exit. True constitutional mercurialism, however, *i. e.*, the disturbances of nutrition, sensation, and even motion, which seriously affect the animal economy, arises most frequently after the long-continued use of small doses of mercury, disappears less speedily, and is probably due to an elimination and deposition of the metal in different organs. These symptoms are observed in their most pronounced forms in workmen who use quicksilver in their occupations, and have been described in a classical manner by Kussmaul (l. c.). They appear more rarely after the medicinal employment of mercury, and in the following remarks only the positively established facts bearing upon this point shall be detailed, without considering the exaggerations of the enemies of the drug.

The *disturbances of nutrition* are always attended with alterations of the general condition, and are due almost exclusively to a direct action of mercury upon the gastrointestinal canal and its secreting glands, and not, as was formerly believed, to its mythical faculty of melting the organs and drying up the blood. The direct involvement of the stomach and intestines is proved by several facts. G. Lewin (l. c.) saw, even after the subcutaneous use of mercury, especially when the proper doses were exceeded, the symptoms of a gastro-enteritis, pain, and burning in the region of the stomach, particularly upon pressure, and diarrhœic stools, sometimes tinged with blood. In keeping with this, the patients felt badly generally; they were pale, and complained of a tired feeling, weakness, and troubled sleep. The explanation of this action upon the intestinal tract is furnished by the fact that, even after subcutaneous injection, mercury is eliminated by this organ.

In agreement with this stand the changes in the digestive canal experimentally produced in animals and also observed in man, which present the picture of catarrhs of

different degrees of intensity, even of ulceration, particularly in the ileum and cæcum. In this simple manner are explained the anorexia, emaciation, vomiting, the pains in the stomach and abdomen, and the failure of the bodily forces, observed in the cases of many persons treated for a long time with small doses of mercury, particularly when one considers that the casting-out of the drug into the intestinal canal, together with the above-described physical anatomical changes in the stomach and intestines, destroys the activity of the digestive fluids. In such persons there occurs, therefore, in consequence of the gradual diminution or loss of appetite, not only a lessened assimilation of food, but this process, when the canal is in a catarrhal condition, is much retarded, under certain circumstances, to such a degree, that, in order to preserve the continuity of the nutritive processes, the body is forced to live upon itself.

This view of the matter is well borne out by the result of the investigations of the nutritive processes made by v. Boeck, in a man who was treated for syphilis by mercurial inunctions. He found no changes in the decomposition of albumen during treatment. In this case, however, the action of the mercury had lasted only sixteen days—a period in which the intestinal changes above described do not usually appear. It must be especially remembered that, for the appearance of disturbances of nutrition, there is necessary either a certain predisposition or a prolonged action of mercury upon the digestive tract.

An alteration in the urine which permits us to draw a conclusion as to the condition of the kidneys sometimes occurs, usually in company with the nutritive disturbances, more rarely alone. It not unfrequently contains albumen, but in small quantities. Since the kidneys, as has been proved, are the organs which eliminate a portion of the mercury, the presence of albumen in the urine is most probably to be attributed to the irritating action of the



drug upon these organs, particularly the uriniferous tubules. The view that this albumen is not due to an alteration of the kidneys, but belongs to the metal which is eliminated in the form of an albuminate, is proven to be unwarranted, by the fact that the urine of persons using the drug always contains mercury and but rarely albumen. The latter always appears when toxic doses are administered, and then substantial alterations can also be found in the urinary passages. In addition to albumen, sugar may also be found in the urine after the use of mercury. This was proven by experiments upon animals made by Saikowski<sup>1</sup> and Rosenbach.<sup>2</sup> In this respect, mercury bears a certain analogy to other poisonous substances, such as morphia, carbonic oxide, etc.

The treatment of the general disturbances of nutrition consists essentially in a removal of the injurious agent and a suitable dietetic regimen. In addition to improving the hygienic relations of the patient, the effort must be made, by the administration of appropriate non-irritating articles of food, to correct any changes which may be present in the intestinal canal, and also to cause a rapid and as complete an elimination of the drug from the body as is possible. The latter end may be reached by producing active diuresis, by means of vapor and sulphur baths, and especially by iodide of potassium, as recommended by Melsens<sup>3</sup> after the use of which a larger amount of mercury is said to leave the body by the kidneys than under ordinary circumstances.

These disturbances of nutrition and the general condition, as is also observed in cases of chronic poisoning with other metals, are frequently only the forerunners of functional disturbances of the general nervous system. Occa-

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<sup>1</sup> Saikowski, Virchow's Archiv, p. 346.

<sup>2</sup> Rosenbach, Zeitschr. f. naturw. Medicin, 3 Reihe, xxxiii., p. 36.

<sup>3</sup> Melsens, Annal. de Physique et de Chimie, III. S., T. 26.



sionally a few of the latter appear during the course of an ordinary treatment by inunction.

The perceptive disturbances comprise not only an alteration of certain psychical attributes and feelings, but also demonstrable peripheral functional changes in the organs of special sense, the touch, sensibility to pain, etc. The individuality of the affected person has a great influence in this regard, so that in one case a central affection of more or less severity is produced as the expression of such a disturbance, while in another peripheral anæsthesia or hyperæsthesia is observed. Among central disturbances, the following have been noticed, even after a subcutaneous injection of mercury: a condition of psychical erethism, appearing at one time as moodiness and increased irritability, at another as terror or timidity, attended with pallor of the face, labored asthma-like respiration, and in some cases irregular heart-action and great weakness. This was first observed by Pearson in persons under treatment by inunction, and also by Lewin in a few instances. The most pronounced cases were observed by Bauer,<sup>1</sup> and also Kussmaul (l. c.) in workmen in mirror-factories. The latter regards this form of affection as specially characteristic of the action of mercury. If the condition persist for some time, there may be developed insomnia, as well as other sensorial phenomena, due to increased irritability of the brain, particularly the *cerebrum*, such as hallucinations and even delirium. These are, however, of a transitory nature, and must not be regarded as independent forms of disease.

Pains in the joints, the face, and the teeth also frequently appear, as well as the opposite condition, diminution of sensibility, in the form of true anæsthesia or analgesia.

Besides the alterations in the domain of sensation, other

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<sup>1</sup> Bauer, Ueber Mercurialismus. Inaug. Dissert., Erlangen, 1860.

mercurial affections occur, which manifest themselves as motor disturbances. These appear most frequently as mercurial tremor, as a rule a chronic affection, but sometimes occurring paroxysmally. At first, the hands and arms are alone affected, as a rule, but gradually, under the continued influence of the drug, the legs, as well as the muscles of the trunk, experience the same fate. Examination of the muscular system, with regard to its electric irritability, reveals in such cases a normal condition, despite the fact that the muscular weakness may be very great. In this respect, as well as by the absence of true muscular paralysis, the effects of mercury show an important difference from those of lead.

As a combination of motor and sensory disturbances, mention must finally be made of the feeling of giddiness which occurs not infrequently, both after the hypodermic injection of large doses of mercury and its external application. Thus, G. Lewin noticed in some of his cases, which had taken large doses of the drug subcutaneously, a remarkable weakness, associated with attacks of dizziness so powerful that the patients were forced to hold fast to surrounding objects in order to avoid falling. These vertiginous attacks, attended with a tendency to fainting, continued even while the patients lay in bed. The identity is complete between these symptoms, appearing after one or more large doses of corrosive sublimate, and the attacks of dizziness occurring after the long-continued use of mercury, which were formerly called mercurial epilepsy.

The symptoms pertaining to the central nervous system are, without doubt, the consequences of a direct action of mercury (called a brain-poison by Kussmaul) upon the affected parts, the transitory effects being produced while the drug is still circulating with the blood, and the chronic in consequence of its deposition in the nerve-centres, and the motor and sensory tracts. With regard to the latter,

the investigations of Pickel<sup>1</sup> should be mentioned. This author succeeded in demonstrating, by dry distillation, the presence of mercury in the brain of a man who had long been treated with the drug. Landerer<sup>2</sup> met with the same success in a case of poisoning by corrosive sublimate. To what extent mercury becomes permanently deposited in the spinal cord and peripheral nerve-distributions has not yet been made the subject of investigation. We must, however, believe that both the transitory as well as the permanent alterations are primarily due to chemical changes in the peripheral and central nervous tissues, which are perhaps not recognizable by the microscope. Histological examination of these tissues, after the use of mercury, has, as yet, yielded but insignificant results. Pleische found a darker color of the gray substance in one case, and Koch of the white in another.

The prognosis of these affections, particularly of the mercurial tremor, depends upon the length of time during which they have existed. It may be favorable when they have lasted only a short time, but is doubtful, even if not absolutely unfavorable, if the patient has suffered from them for a long period.

The treatment is in the main the same as that of the general disturbances of nutrition, and should therefore be directed to the removal of the mercurial influence, and as complete an elimination as possible of the drug from the body. In addition, cold frictions, douches, sea-baths, and the simultaneous use of nervines are indicated in conditions of erethism also. The electric current should be tried for the relief of anæsthesia and analgesia.

#### ACIDUM ARSENIOSUM.

The similarity of physiological action of the different

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<sup>1</sup> Pickel : Buchner's Toxicologie, 1822, p. 433.

<sup>2</sup> Landerer : Buchner's Repertor., III. Reihe, Bd. 25, p. 248.

preparations of arsenic shows itself also in the incidental effects which follow the occasional or repeated use of this drug, and we shall therefore consider only arsenious acid, which may serve as the prototype of all the arsenical preparations.

Binz and Schulz<sup>1</sup> have recently shown that if arsenic acid is digested for several hours at a temperature of 38° C. (101° F.), with fresh fibrin, brain, white of egg, or pancreas, it appears in the dialysate as arsenious acid, and after administering arsenious acid to animals, they found arsenic acid in the watery contents of the intestines, and, *vicê versâ*, arsenious acid after giving arsenic acid. These processes of oxidation and reduction, according to these authorities, take place in the glands, the protoplasma of the nerve-centres, and in all other cells in which the conditions necessary for the occurrence of such actions are found. In consequence of this constant transfer of nascent oxygen within the molecules of the living albumen, the living cells burn more actively than during ordinary tissue-changes, and upon this local increased combustion depend all the manifestations of the action of arsenic.

This explanation also facilitates the comprehension of a part of the effects, lying outside physiological limits, which appear in man after the internal or external use of arsenic.

This applies especially to the effect upon the skin which may be produced by the internal or external use of the drug in man and animals. This action of arsenic was known even to physicians of antiquity. Thus Paulus Ægineta<sup>2</sup> writes: "*Arsenici vis est caustica, utuntur eo in pilis abolendis, quod si diutius adhæserit etiam cutem ipsam attingit.*" If arsenious acid in watery solution, or

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<sup>1</sup> Binz und Schulz, *Archiv f. experimentelle Pathol. u. Pharmacol.*, Bd. xi., p. 200.

<sup>2</sup> Paulus Ægineta: *Opera*, ed. J. Guinterius, Lugduni, 1551, p. 479.

in the form of a salve or a paste, remains for some time in contact with the healthy skin, an inflammatory irritation appears, attended with pricking or burning pains and mild fever, and vesicles or pustules may form on the reddened and swollen surface, without the appearance of systemic absorptive effects. If the inflammation increases, an erysipelatous swelling, and, subsequently, discolored sanguinolent eruptions may, according to Falck,<sup>1</sup> mark the beginning of general poisonous effects, in the same manner in which they follow the internal administration of arsenic, as will presently be described. This is also the case if the agent is applied to the surface of wounds. The hairs on the affected surfaces fall out, as a rule. The eruptions heal with exfoliation of the epidermis in large flakes.

Entirely analogous changes of different kinds in the skin have been seen after the internal use of arsenic in ordinary medicinal doses, particularly in the form of the usually employed Fowler's solution. How varied these affections may be is seen from the homœopathically-inspired description of Imbert Gourbeyre.<sup>2</sup> He says: "Eruptions pétéchiales ou ecchymoses, éruptions papuleuses, ortiées, vésiculeuses, érysipélateuses, pustuleuses . . . telles sont les principales formes de l'arsenic exanthématogène dans ses manifestations à la peau." In accordance with this, different authors describe the arsenic eruptions differently. Thus, Macnal<sup>3</sup> reports a rubeola-like exanthema in patients who, for three days, had taken only 0.18 gram (gtt. iiij.) of Fowler's solution. Pereira, in a case of gout, for which he had prescribed 0.01 gram (gr.  $\frac{1}{6}$ ) of the arsenite of potassium daily, saw on the third

<sup>1</sup> Falck: Die klinisch wichtigen Intoxicationen, Virchow's Path. u. Therap., Bd. i., p. 254.

<sup>2</sup> Imbert-Gourbeyre, Gaz. méd. de Paris, 1862, p. 227, and Etude sur quelques Symptomes de l'Arsenic. Paris, 1862.

<sup>3</sup> Macnal, Medical Times and Gazette, 1868.



day, after a sleepless night with headache and feeling of increased warmth of the skin, an intensely red eruption on the face, the neck, the upper part of the body, and the flexor surfaces of the joints, with œdema of the eyelids. The eruption disappeared between the third and fifth days, while the desquamation lasted nearly two months, and occurred in large flakes. When, after the disappearance of all the symptoms, arsenic was again administered, the same phenomena again showed themselves, accompanied with profuse salivation. According to Imbert Gourbeyre, the eruption appears by preference on the neck, face, and genital organs, and also on the hands. The papules, of pin-head size, which compose it, appear at first in scattered groups, but unite later and form patches as large as a bean and larger. This author, like Pereira, says that the eruption lasts for six or eight days, but he saw only a branny desquamation of the epidermis after it.

How small a dose suffices to produce an eruption is shown by a case reported by Bazin,<sup>1</sup> in which ecthyma-like pustules appeared after the consumption of 0.05 gram (gr.  $\frac{5}{100}$ ) of arsenic during fourteen days.

In this connection, mention should be made of the statement of Wyss,<sup>2</sup> that he saw alopecia areata develop on a boy after the prolonged internal use of arsenic. He utilizes this observation to establish the view that this disease is due to a disturbance of nutrition of the hair-follicles; and not to the presence of a fungus, as recent observers seem again inclined to believe.

If we review the facts here detailed, bearing upon the action of arsenic upon the skin, it cannot be denied that the changes in this organ, produced by the external and internal use of the drug, are identical. After its internal administration, therefore, there must occur in certain cases

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<sup>1</sup> Bazin: *Leçons sur les affections cutanées artificielles*. Paris, 1862, p. 196.

<sup>2</sup> Wyss, *Archiv f. Heilkunde*, Bd. xi., 1870, p. 17.



a penetration of the arsenic into the skin, and a partial elimination of the drug by this organ. This is in fact the case, as is shown by the experiments of various authors.

Chatin<sup>1</sup> succeeded in finding arsenic in the contents of a bulla produced by cantharides upon the skin of a person poisoned with arsenic.

Barella<sup>2</sup> proved the direct elimination of arsenic by the sweat-glands, especially when the skin acts vicariously for the kidneys, while Bergeron and Lemattre<sup>3</sup> demonstrated that combinations of arsenious acid with alkalies could be cast out with the sweat, while, on the other hand, the arsenite of iron is so split up in the body that the iron passes into the urine, while the arsenic appears in the sweat in the form of arsenite of potassium.

In view of these facts, we must regard the skin affections already described, no matter by what method of administration of the drug they were produced, as due to a direct local action of arsenic, and must seek the ultimate reason of their occurrence, according to Binz and Schulz, in a local increased combustion in the living cells.

Since the arsenical eruption, as has already been stated, disappears spontaneously in a few days, therapeutic interference with it is hardly necessary. In cases in which the inflammation of the skin has attained serious dimensions, or has taken on a malignant character, it will be necessary, in addition to furthering the elimination of the poison through the kidneys by means of diuretics, to resort to local antiphlogistic treatment, and in case products of decomposition are present, to proceed antiseptically.

Much more frequently than the phenomena thus far described, there appear after the internal use of arsenic for a shorter or longer period, according to the individu-

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<sup>1</sup> Chatin, *Jour. de Chimie médicale*, 1848, p. 328.

<sup>2</sup> Barella, *Jour. de Médecine de Bruxelles*, Juillet, 1863.

<sup>3</sup> Bergeron and Lemattre, *Archiv génér. de Médecine*, 1864, Vol. ii., p. 173.

ality of the patient, irritation of the mucous membranes of the mouth, throat and stomach, and consequently digestive disturbances. The tongue in such cases is thickly coated, and there appear an unpleasant burning in the mouth, thirst, a feeling of oppression in the stomach, loss of appetite, eructation and even vomiting. The affection of the mouth may assume the character of an angina or stomatitis, and not infrequently free salivation is observed after very small doses of arsenic have been taken. Harles<sup>1</sup> first discussed this fact in the following words: "*Diutius continuato arsenici usu satis parco excitatur haud ita raro salivæ aliquanto largior secretio, sive ptyalismus levior species.*" In modern times, similar statements have been made by Imbert-Gourbeyre (l. c.) and Trousseau and Morganti,<sup>2</sup> among others.

This irritation of the buccal mucous membrane spreads not infrequently to the air passages, resulting in the production of a dry cough, bronchitis, and harshness of the voice. If the nasal mucous membrane be attacked, there appear burning in the nose and coryza and (although but rarely), as Heim<sup>3</sup> first observed, epistaxis.

If the tear-ducts and conjunctivæ become affected in consequence of the extension of the catarrhal process (which occurs quite frequently), the patient suffers from a flow of tears, photophobia, amblyopia, and sometimes swelling of the eyelids and the usual symptoms of conjunctivitis, the objective included. Very rarely an icteric discoloration of the sclerotic is observed—a phenomenon which is tolerably common, in connection with xanthopia, in acute arsenical poisoning.

As nervous symptoms there appear in some cases headache, buzzing in the ears and giddiness.

<sup>1</sup> Harles: *De usu arsenici*, Norimbergæ, 1811, p. 301.

<sup>2</sup> Morganti, *Gaz. med. de Paris*, 1852.

<sup>3</sup> Heim: *Vermischte Schriften*; 1836, p. 302.

It must finally be mentioned that it has been stated by French authors, such as Charcot<sup>1</sup> and Devergie,<sup>2</sup> that anaphrodisia not seldom follows the use of Fowler's solution. This diminution of the sexual instinct disappears after the discontinuance of the drug.

The treatment of the symptoms described consists in the immediate withdrawal of the drug and the use of demulcents for the affected mucous membranes. Since all the above-described pathological processes cease spontaneously a short time after the discontinuance of the remedy, it can hardly become necessary to attempt antidotal treatment with hydrated magnesia, or the hydrated sesquioxide of iron. From a prophylactic stand-point, however, care must be taken that the arsenic is not administered upon an empty stomach, that the usual doses are not too rapidly increased, and that its use is not too long kept up.

#### AURI CHLORIDUM. AURI ET SODII CHLORIDUM.

The chloride of gold, which, like the officinal chloride of gold and sodium, has been highly praised and much employed as a specific for syphilis,<sup>3</sup> causes very frequently, according to the observations of Chrestien,<sup>4</sup> even in doses of 0.006 to 0.003 gram (gr.  $\frac{1}{10}$  to  $\frac{1}{20}$ ), a feeling of burning and heat in the skin, gastric disturbances, colic and diarrhœa. The chloride of gold and sodium, according to Wibmer, causes, even in doses below the established maximal limit, headache, sleeplessness, dryness in the mouth, oppression in the region of the stomach, and diarrhœa.

Others have noticed, after the use of this drug, salivation, increased secretion of urine, and exaggerated sexual activity.

<sup>1</sup> Charcot, *Bullet. de Thérapeut.*, lxvi., p. 529.

<sup>2</sup> Devergie, *Eod. loc.*, lxvii., p. 175.

<sup>3</sup> Legrand, *Bulletin de Thérapeutique*, Décembre, 1846.

<sup>4</sup> Chrestien: *De la méthode iatraleptique*, IIième édit. Paris, 1803.

The gastric disturbances are explained by the fact that albumen is precipitated by the salts of gold, and that the double compounds of the chloride of gold with the chlorine alkalies are readily soluble. They present a close resemblance to the disturbances produced by other metals, and are due to the action of the drug upon the tissues, particularly the mucous membranes of the *primæ viæ*.

## PHOSPHORUS.

Even one small dose, 0.002 gram (gr.  $\frac{1}{30}$ ), of phosphorus may produce in certain cases nausea or vomiting, a sense of weight or pain over the stomach, and in rare instances icterus, which may persist, it is said, for weeks or months. This abnormal action of the drug may be due to the method of administration, for it is known that phosphorus, taken in pilular form or in oil, remains longer in the stomach than when it is given in a more readily absorbed menstruum, such as chloroform, etc., and this long-continued absorptive process may readily excite irritation of the digestive organs. For this reason Dujardin-Beaumont,<sup>1</sup> who in *tabes dorsalis* prescribed the remedy dissolved in chloroform, in capsules, witnessed the occurrence of digestive disturbances only after the uninterrupted use during eight or ten days, of 0.003 to 0.004 gram (gr.  $\frac{1}{20}$  to  $\frac{1}{16}$ ). The symptoms disappeared after the temporary suspension of the drug, or diminution of the dose.

## IODINIUM.

In consequence of the extraordinary curative powers of iodine and its compounds, and its extensive therapeutical employment, the attention of physicians was long ago (1820) directed to certain bodily changes, which now and then showed themselves during its administration. It is

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<sup>1</sup> Dujardin-Beaumont, Wiener medicinische Wochenschr., 1868, p. 767.

true that a long time elapsed before these incidental effects of iodine obtained general recognition, and controversies over the existence of such a thing as an "iodine-disease," or "iodism," or as to whether its symptoms were to be referred to other causes, fill many a page of pharmacological literature. Enlargement of the thyroid gland, among other affections, was early subjected to treatment by iodine internally and externally, and hence abnormal effects of the drug were frequently observed in this affection. There was, therefore, no lack of authors<sup>1</sup> who denied the occurrence of such effects when the drug was used in other diseases, and attributed the symptoms which so frequently appear during the treatment of goitre with iodine, to "absorption of the organic substances contained in the thyroid gland." The occurrence of iodism was also denied on more reasonable grounds. Thus Hjaltelin<sup>2</sup> observed that the inhabitants of Iceland, especially those living on the coasts, made use of a diet composed principally of algæ belonging to the class of *Laminariæ*, which are very rich in iodine, in the manufacture of which they are largely employed. Some persons consume 200 to 250 kilos (437 to 547 pounds) of these dried plants yearly. Therefore, since 50 kilos (110 pounds) of these algæ contain at least 250 grams ( $\frac{2}{3}$  viij.) of iodine, these people consume annually 1 to  $1\frac{1}{4}$  kilo ( $2\frac{1}{5}$  to  $2\frac{1}{2}$  pounds) of iodine, or about  $1\frac{1}{2}$  kilo ( $3\frac{1}{4}$  pounds) of iodide of potassium. In spite of the consumption of these large quantities of iodine, Hjaltelin noticed in such cases no phenomena which could be attributed to iodism. However plausible these deductions may seem, but little weight should be attached to them; for aside from the fact that the quantity of iodine in sea-

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<sup>1</sup> Röser, Ueber die sogen. Jodkrankheit, richtiger Krankheit der vertriebenen Kröpfe. Würtemb. medic. Correspondenzbl., 1844, No. 31, and Archiv f. physiol. Heilkunde, Bd. vii., 1848, p. 74.

<sup>2</sup> Hjaltelin, Allgem. medic. Centralzeitung, 1853, p. 745.



weed is stated to be five times as great as it really is, the circumstance has not been taken into consideration that only a relatively small quantity of the plants and their constituents, as is the case with all vegetables, is taken up into the fluids of the body, while by far the greater part is not utilized, but is discharged with the fæces. For this reason these coast-dwellers take into their systems only very small quantities of the iodine which is so firmly held in the plants. It would lead us too far to consider all the other objections which have been raised in this connection. It is now positively established that iodine and its salts, after its internal or external use, once or repeatedly, in different doses, is capable of exciting changes in various organs or in the general condition, but only in those who are especially predisposed to such occurrences.

The external application of preparations of iodine causes injurious incidental effects only, when they contain free iodine, as is the case with ointments of iodide of potassium which have turned yellow, Lugol's solution, or the

*Tincture of Iodine.*—The local physiological action of this preparation upon the healthy skin and mucous and serous membranes is well known. It is identical with that of the vapor of iodine. The intact skin, under the influence of the irritation, is the seat of a feeling of warmth, burning and pricking, becoming at first yellow, and, after renewed applications, of a dark brownish-red color; then dries up and becomes shrivelled, and, after some time, the epidermis can be torn off in large flakes. With this normal process there are not unfrequently associated incidental effects, either on the parts treated or on distant portions of the skin, in the form of exanthematic affections. There appear either rubeola-like, or papular, pustular, or even bullous eruptions, which soon heal, with desquamation, when the use of the agent is discontinued. Thus, A. Simon and Regnard,<sup>1</sup> among others, observed, after the

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<sup>1</sup> Simon and Regnard, *Gaz. médic. de Paris*, 1874, p. 262.



application of tincture of iodine with glycerin to the eczematous scalps of children, an extensive papular eruption on the face and other parts of the body. This observation is confirmed by Badin.<sup>1</sup> This author never succeeded in producing albuminuria in adults by painting the skin with tincture of iodine; while the application of the agent to portions of the healthy skin not larger than the palm of the hand excited this condition in children eight or nine years of age. He believes that this difference is due to the greater absorptive power of the infantile skin, which permits the iodine to enter the circulation as such; while in adults, in whom absorption by the skin takes place more slowly, it is taken up in the form of the iodide of sodium or potassium. This explanation cannot, however, be accepted, in view of the disturbances of the urinary apparatus still to be described, which occur after the use of iodide of potassium also.

It will be readily understood that in the local action of this agent upon portions of skin deprived of epidermis, as well as upon the surfaces of wounds and mucous membranes, the subjective sensations, as well as the local changes, are much intensified. The pains resulting from the irritation, which almost equals a cauterization, are very severe, although of a transitory nature. The iodine coagulates the secretions upon the wound-surfaces or in serous cavities, because it enters directly into combination with albumen or albuminoid substances, and may, therefore, excite violent inflammation, with subsequent exudation or suppuration. In this case, also, eruptions may appear on distant parts of the body—a circumstance which proves that iodine may be absorbed from all the parts mentioned, and afterwards act upon the skin.

But the absorption also manifests itself in another unde-

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<sup>1</sup> Badin : De l'albuminurie consécutive aux applications de teinture d'iode chez l'enfant. Paris, 1876.

sirable manner after its external application, viz., by the appearance of more remote effects upon certain organs and their functions, as well as by a number of symptoms affecting the body at large. These are, therefore, in part, identical with those phenomena which often appear after the internal administration of iodine-compounds. Simon and Regnard (l. c.), in addition to the papular eruptions already mentioned, noticed coryza and epistaxis after the application of iodine. In fourteen cases, they also observed albuminuria four times, and found iodine in the urine. The albuminuria appeared and disappeared with the use or discontinuance of the drug: Buckell<sup>1</sup> reports that in the case of a lady, who had the tincture of iodine very lightly painted upon a tumor between the scapulæ, there appeared pain and a sense of oppression in the epigastric region, and also trembling, weakness, profuse sweating, dribbling of urine, and inability to stand erect. The use of stimulants and the application of warmth over the stomach caused these symptoms to disappear in a few days. Nélaton,<sup>2</sup> after opening a cold abscess upon a man, injected two syringefuls of a dilute solution of iodide of potassium. Two hours later, there appeared vesical disturbances, vomiting, thready pulse, swelling of the upper eyelids, pain in the larynx, and on the next day, aphonia, croupy cough, and prostration. The administration of ice and cathartic pills, and the application of mustard-plasters to the extremities and blisters on both sides of the neck, caused these symptoms to disappear in three days. Fonssagrives<sup>3</sup> has reported a similar case. Two hours after the injection of a small quantity of the officinal tincture of iodine, diluted one-half, into a traumatically-inflamed tunica vaginalis (the fluid which it contained

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<sup>1</sup> Buckell, *The Lancet*, 1st Feb., 1843.

<sup>2</sup> Nélaton, *L'abeille médicale*, 15 Novembre, 1853.

<sup>3</sup> Fonssagrives, *L'union médicale*, 1860, No. 71.

having been previously withdrawn), he witnessed the occurrence of a swelling of the scrotum, attended with high fever. During the remainder of the day there also appeared irritation of the bronchial tubes, discharge from the nose, redness of the eyes, œdema of the epiglottis, and increased flow of saliva. The fever lasted five days.

More varied than these more acute symptoms appearing after the external application of iodine, are the incidental effects which follow the shorter or longer internal administration of the drug in medicinal doses. The iodide of potassium being generally resorted to for the internal administration of iodine, we shall in this connection consider this agent as a representative of all the other compounds of iodine.

#### POTASSII IODIDUM.

The first comprehensive data concerning "iodism" were published by Rilliet,<sup>1</sup> who distinguishes three forms of the affection. According to him, the first occurs acutely in all persons of all ages, after large doses, and is due to the irritation produced by the agent in the gastro-intestinal canal. The second requires a certain predisposition of certain organs, and develops gradually in the form of slight nervous disturbances, anomalies of secretion of different mucous membranes, and affections of the skin. The third appears as an iodine-cachexia or constitutional iodism, comprises a number of disturbances of the general condition and nutrition, and occurs after the prolonged use of even minimal doses. Practical observation has, however, shown that such a sharp distinction between the different varieties of the affection is not possible, because first one and then another group of symptoms appears in combination, and also because, in a given case, small doses may produce incidental effects, which are usu-

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<sup>1</sup> Rilliet, *Bullet. de l'Académie de Médec.*, 1860, p. 332.

ally seen only after large doses, and *vicê versâ*. It is, therefore, evident that, for unknown reasons, sometimes one organ and sometimes another is affected in its functions, or experiences material changes through the action of iodine. We are not, however, in a position to construct laws from this circumstance, because we are ignorant of the conditions necessary for the production of these affections. We must, therefore, content ourselves with studying in detail the various effects produced by iodine upon individual organs.

After taking iodide of potassium, many persons experience, particularly after waking in the morning, an astringent metallic and bitter taste on the tongue. This quickly disappears, as Laroche<sup>1</sup> states, after washing the mouth with cold water, to which a dessert-spoonful of spirits of horse-radish has been added. In very sensitive persons, there is also occasionally observed, after small doses, tickling and burning, and a sensation of dryness and constriction of the pharynx. In rare cases, disturbances of the power of swallowing are observed. The sensation of burning may extend from the throat down the sternum to the region of the stomach. With this there is frequently associated increased flow of saliva, in consequence of the peculiar power of iodide of potassium to excite the secretion of nearly all the glands.

Although the function of the stomach is not affected by one or more small or medium doses of iodide of potassium, even an increase of the appetite to intense hunger being sometimes noticed, there is occasionally observed, in the case of persons who have a pronounced antipathy to this drug, nausea and vomiting, and in others, as Ricord<sup>2</sup> states, a pain seated at the fundus of the stomach, not increased by pressure, and without influence upon diges-

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<sup>1</sup> Laroche, Canstatt's Jahresbericht f. d. ges. Medicin, 1844, IV., p. 195

<sup>2</sup> Ricord, Bulletin générale de Thérapeut., 1842, p. 161.

tion. Rabuteau attributes these phenomena to adulteration of the iodide of potassium (IK) with the iodate of potassium ( $KIO_3$ ). He claims that, in this case, in consequence of the influence of the gastric acid, free iodine is formed in the stomach, and attacks the mucous membranes. Although the hypothesis is not altogether satisfactory, in view of the fact that these symptoms occasionally show themselves after taking the pure iodide of potassium, it is nevertheless possible that in some cases the freshly-liberated iodine may favor their occurrence. Therefore, in case doubts arise as to its purity, the iodide of potassium should be tested for the presence of the iodate, in the manner to be described later.

Digestive disturbances occur only after the long-continued use of large doses of the iodide of potassium. The irritative effects of the drug upon the mucous membranes of the air-passages, on the other hand, take place so readily, that perhaps a majority of those who take it suffer from them in a greater or lesser degree. This action is primarily exerted upon the mucous membrane of the nose, but it often occurs simultaneously upon that of the larynx, and the bronchial tubes and their ramifications.

Since the affection first became known, the changes in the nose have been called "iodine-cold." It manifests itself in the form of a catarrhal inflammation of the mucous membrane of varying intensity, and may spread over its whole surface, invading the choanæ, the frontal sinuses, and the antra of Highmore. The membrane in such cases is softened and swollen, secretes freely, and the subjective symptoms, which often begin with a burning sensation in the nose, take the form, later on, of a feeling of oppression and occlusion, sneezing, etc. If the olfactory region is particularly affected, loss of smell also occurs. The whole affection ends soon after the discontinuance of the drug.

In the description of the acute pathological symptoms produced by the external application of iodine, the occur-



rence of œdema of the glottis has already been mentioned. The tendency of the preparations of iodine to excite catarrhal conditions of mucous membranes makes it probable that this œdema is due to a sudden swelling of the membrane of the affected parts, with a subsequent infiltration of the submucous connective tissue. The irritation of mucous membranes of parts more deeply situated which occurs in many persons after the use of small doses of iodide of potassium renders this view more probable. Thus Ricord (l. c.) often observed in such cases a bronchitis which could be physically demonstrated, attended with labored respiration, cough with oppressed breathing, pains in the breast and tolerably free expectoration, which, however, never became putrid. These respiratory disturbances have been by some authors<sup>1</sup> needlessly designated as "iodine asthma," in analogy to those previously described as asthmatic, occurring after the use of lead, mercury, and other metals. But even true œdema of the glottis, as has been proven by the observations of Petitjean,<sup>2</sup> may be produced by medicinal doses of iodide of potassium, but only in persons already suffering with laryngeal affections before taking the drug. In the case of an individual who died from such an œdema of the glottis, there were found small ulcers in the larynx, as well as œdema of the epiglottis. That pre-existing organic changes may be made worse in this manner is proved by a case reported by Rodet,<sup>3</sup> of a man suspected to have tuberculosis, who every time he took iodide of potassium had a more or less profuse hæmoptysis.

From an extension of the catarrhal irritation to the vocal cords there occurs in very exceptional cases difficulty in phonation, without deeper lesions.

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<sup>1</sup> Santlus, *Deutsche Klinik*, 1856, p. 18.

<sup>2</sup> Petitjean: *Accidents du côté de la peau et des muqueuses déterminés par l'administration de l'iode de potassium*. Paris, 1879, p. 29.

<sup>3</sup> Rodet, *Gazette médicale de Paris*, 1849, p. 946

Analogous to the pathological changes on the mucous membrane previously named, are those which appear with tolerable frequency on the eyes and their appendages after the use of iodide of potassium. These rarely appear entirely alone, but are usually attended with nasal or bronchial catarrh, and occur suddenly in one or both eyes, and manifest themselves immediately, in part as a catarrhal irritation of the conjunctiva and the lining membrane of the lachrymal gland and duct. The vessels of the palpebral and bulbar conjunctiva are greatly injected, the mucous membrane itself is swollen and softened, the flow of tears is increased, but photophobia occurs but rarely; on the other hand chemosis and œdema of the eyelids sometimes take place. The subjective symptoms vary with the degree of the affection. The patients usually complain of burning and itching, and have a feeling as if a foreign body were in the eye. In some cases, a painful sensation of weight is experienced in the supra-orbital region, at the point of exit of the supra-orbital nerve.

These incidental effects of iodide of potassium may, according to the specific disposition of the individual, appear after either one or repeated doses. They usually show themselves after the frequent use of small doses, and disappear spontaneously a few days after stopping the drug, without leaving after-effects, and still more quickly if mildly astringent lotions are used. Many cases have been described in which the above-mentioned symptoms appeared after 0.5 gram (gr. viiss.) and even less, of iodide of potassium. Thus Mecklenburg,<sup>1</sup> among others, witnessed after 0.5 gram (gr. viiss.) of this drug, in the course of a few hours, intense pains in the eyes, abundant flow of tears, burning in the nose and throat, as well as swelling and livid discoloration of the upper eyelids, particularly in the tarsal region. Twenty-four hours later, all these

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<sup>1</sup> Mecklenburg, Berl. klin. Wochenschr., 1866, p. 262.

phenomena had disappeared. When only 0.25 gram (gr. iv.) of iodide of potassium was again taken, the same symptoms, with the exception of the swelling of the eyelids, reappeared in four hours.

In addition to the purely external phenomena already described, it is said that there sometimes appears, although very rarely, a limitation of the power of accommodation, as well as diminution of the sharpness of sight, symptoms of presbyopia. Corlieu<sup>1</sup> reports such a case. He observed, in addition to other abnormal effects of iodine, presbyopia with dilatation of the pupils and a suddenly-occurring hypermetropia, symptoms which passed away a few days after stopping the iodine. Dorval<sup>2</sup> also observed diplopia with dimness of sight, and Brera<sup>3</sup> the latter symptom associated with orbital pain. Which of the possible factors was instrumental in causing these disturbances of function has not yet been positively determined.

The already-described irritative effects upon the skin, occurring upon distant parts of the body after the external application of iodine, also show themselves in many cases after the internal administration of the iodide of potassium, under widely-varying conditions as regards the dose and length of time during which the drug was used. In the latter case, however, the multiformity of the eruptions is much more marked than in the former. This particular incidental effect of the iodide of potassium has been well known ever since its introduction into the materia medica, and one therefore finds almost innumerable observations on this subject in literature. They all go to establish as a fact that the iodide of potassium often produces eruptions, from simple erythema to petechiæ, with or without fever, occurring either alone or in combination with other ab-

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<sup>1</sup> Corlieu, *Gazette des hôpitaux*, Juin, 1856.

<sup>2</sup> Dorval, *eod. loco*.

<sup>3</sup> Brera, *eod. loco*.

normal effects of iodine, and disappearing, as a rule, very soon after the use of the remedy is suspended.

These eruptions, according to Fischer,<sup>1</sup> are divisible into four principal forms.

I. *The erythematous form*.—The skin, particularly on the forearms, and also on the face, is reddened, either diffusely or on circumscribed spots, and its temperature elevated. After discontinuing the drug, this symptom disappears in a few hours, but if its use be persisted in, the eruption may pass into that which is most common,

II. *The urticaria-like form*.—Usually on the abdomen and extremities, but also on other parts of the body, there appear, without fever, intensely red wheals, but slightly raised, surrounded by an areola, generally collected into groups, only distinguishable from a genuine urticaria by their more intense color, which is usually described as rose-red, and which become pale on pressure. They disappear after the use of iodine is stopped, without desquamation.

III. *The nodulo-pustular form*.—This is more rarely observed, and occurs most frequently in scrofulous individuals, usually upon the upper half of the body. An itching spot forms, of a deep-red color, which is soon transformed by exudation into a papule, or a bluish-red nodule, with or without an areola. This may persist, but as a rule there is developed upon it a colored vesicle filled with clear fluid, or a pustule, which may burst or dry up, while the papule, after the cessation of the use of the iodide of potassium, slowly disappears with desquamation, often leaving behind a bluish-red or marbled pigmentation of the skin.

As intermediate forms pure vesicles, acne-like pustules (iodine-acne), and even furuncles are observed. Thus Brshesinsky<sup>2</sup> witnessed, in the case of a woman who took

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<sup>1</sup> Fischer, Wiener medic. Wochenschr., 1859, No. 29, p. 470.

<sup>2</sup> Brshesinsky, Canstatt's Jahresber. f. d. ges. Medicin, 1843, iv., p. 32.

three times daily thirty drops of the tincture of iodine, the development of large furuncles with intense surrounding inflammation, on the breast and between the shoulder-blades. After warm applications they fell off in the form of lumps, leaving large ulcers behind.

IV. *The eczematous form.*—This is very rare, and appears especially on the hairy scalp and in the neighborhood of the scrotum. The differential diagnosis between syphilis of the skin and this affection is easily made, especially in view of the fact that the latter disappears soon after the discontinuance of the drug.

In this connection, for the sake of completeness, mention should be made of a form recently described, viz.:

V. *The petechial form.*—Fournier<sup>1</sup> describes this eruption, which he calls iodine purpura (jodisme pétechiale) as very rare. He saw the eruption, which has also been mentioned by Ricord, in the majority of the cases during the first three days after the use of iodide of potassium, more rarely from the third to the sixth day. In some individuals it always appeared as soon as iodine was administered, and in the case of one patient a new eruption occurred every time the dose was increased. It appeared in every case exclusively on the legs (once only on the trunk) more profusely on the extensor than on the flexor surfaces. It never attacked the knees or the feet. There are usually as many as one hundred discrete patches on each leg. They are miliary, usually of pin-head size, rarely as large as a bean, and cause no general disturbances of any kind. The eruption usually reaches its height in two to three days, and lasts at most two to three weeks, and then disappears. Petitjean<sup>2</sup> confirms these details in the main, but describes a case in which the eruption also occupied the dorsal surface of the foot.

<sup>1</sup> Fournier, *Revue mens. de Médecine*, 1877, p. 653. *Vierteljahrsch. f. Der. u. Syph.*, 1878, p. 294.

<sup>2</sup> Petitjean, *l. c.*, p. 35.



Ausspitz<sup>1</sup> saw a similar eruption in a patient who had taken twenty-five iodide of potassium pills, each containing 0.2 gram (gr. iiss.) or in all five grams (gr. lxxv.)

The best explanation of the occurrence of the above described incidental effects of iodide of potassium is found in the view that they are all due to a direct influence of the drug (or its products of decomposition) upon the affected parts, which it reaches through the blood. The hypothesis of "a saturation of the body with iodide of potassium," formerly held by the majority of authors, of which these symptoms were considered as the expression, is both so obscure and inexact, and so easily refuted by the fact that these affections may occur after quite insignificant doses, that it is unworthy of further discussion. The results of chemical analysis also speak in favor of the local origin of these phenomena.

It has long been known that iodine can be found in various secretions, *e. g.*, the urine, saliva, sweat, milk, and tears, a short time after taking iodide of potassium. Adamkiewicz<sup>2</sup> also succeeded in demonstrating its presence in the nasal mucus and in the contents of the sebaceous glands in cases of iodine acne, thus showing that the differential diagnosis between this affection and ordinary acne may be made by chemical means. In view of this discovery, Adamkiewicz attributes iodine acne to the action of iodine upon the sebaceous glands. He believes that the disease is due to the fact that the salt of iodine which is taken into the body forms free iodine in combination with the nitrate of ammonium present in the stagnant secretions of the skin, and this may irritate the glands and the surrounding tissues. The iodine which is discharged with the sweat does not produce this affection, as is shown by the well-known fact, that the palms of the hands

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<sup>1</sup> Ausspitz, Vierteljahrsch. f. Dermatolog. u. Syphilis, 1878, p. 294.

<sup>2</sup> Adamkiewicz, Charité-Annalen, iii., 1876.

and soles of the feet are not affected by iodine acne. That iodide of potassium should choose these unusual channels of exit from the body, instead of the ordinary ones, may be due to individual peculiarities, or to the fact that the urinary passages, although in a physiological condition, perform less work than usual, as in summer, or that they are diseased.

Thus Johnson<sup>1</sup> saw in many cases of Bright's disease, in which small doses of iodide of potassium were given, pustular iodine eruptions, and Rose,<sup>2</sup> after the injection of preparations of iodine into an ovarian cyst, found a large quantity of the drug in the fluids which were vomited soon afterwards. In the latter case, there probably occurred an elimination of the drug into the stomach, in consequence of a diminished secretion of urine.

The fact observed by Simon and Regnard (l. c.) that albuminuria sometimes results from the external use of iodine, goes to prove that this substance may exert a direct action upon the urinary passages. Iodide of potassium is said to produce a similar effect in some persons. Rodet (l. c.) and Petitjean (l. c.) have reported cases in which vesical tenesmus, dysuria, retention of urine, and even hæmaturia, followed the use of this salt.

The old and familiar experience that iodine possesses the power of reducing hyperplasia of glandular tissue, finds a physiological analogy in the effect of long-continued medicinal doses of iodide of potassium upon the testicles, ovaries, and mammæ. Many authors claim to have witnessed under its use the occurrence of varying degrees of atrophy in these organs, although they were previously in a normal condition. It is probable that a direct localized action of the iodine salt or iodine upon the cellular elements of the gland is largely instrumental in producing such results.

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<sup>1</sup> Johnson, *British Medical Journal*, Jan., 1859.

<sup>2</sup> Rose, *Virchow's Archiv*, Bd. 35, 1864, p. 32.

As regards the genital system, it is said that increase of the sexual appetite, a discharge of semen, and in women more abundant menstruation, may result from the protracted use of the iodide of potassium.

Mention must finally be made of the disturbances of the general nervous system and of nutrition which occur in some persons after the use of iodine—that group of symptoms which Rilliet has designated constitutional iodism. This condition, according to him, may follow the protracted use of even minimal doses of the iodide of potassium. The patients present a peculiar cachectic color of the skin, and become much emaciated, although their appetite is usually good. This condition shows itself in the face and about the hips, breast and scrotum, and is associated with a feeling of lassitude and physical weakness, and a kind of cerebral confusion which has been called “*ivresse iodique*” by French authors. The patients also suffer from derangements of hearing, lancinating pains in the extremities, slight spasms of the tendons, and nervous palpitation of the heart.

Although the facts detailed prove that iodide of potassium often fails to act in a normal manner, causing instead undesired incidental effects in the most different organs, this circumstance would not justify us in limiting the use of this drug, as Rodet proposed, to a small number of diseases. For these phenomena are observed in only an insignificant number of persons, and in the large majority of instances they are of merely temporary duration.

This fact does not exclude the necessity of observing a certain amount of caution in administering this remedy, especially in cases which already suffer from diseases of the larynx or kidneys, and the discontinuance of its use on the first appearance of undesirable incidental effects.

If disorders of the intestinal tract, such as vomiting, diarrhœa, etc., appear immediately or a short time after taking the drug, it would be advisable to test the purity

of the solution used, for which purpose it should be decomposed with hydrochloric or sulphuric acid. If the iodate of potassium be present, a precipitate is thrown down, and free iodine is formed.

### BROMINUM.

On account of its disagreeable physical qualities, bromine is but seldom employed therapeutically. It is, however, occasionally used by inhalation, and in watery solution as a gargle in infectious diseases, such as diphtheria, etc. Besides, on the recommendation of Liebreich, living-rooms, which are suspected of being infected, are sometimes purified by spontaneously volatilizing bromine—a method which is certainly preferable to all others, when the apartments can be closed and allowed to remain unoccupied for a long time. For bromine, which, in solution, acts as a caustic upon the skin and mucous membranes, in the form of a gas irritates the mucous membranes with which it comes in contact, exciting changes varying from slight redness to violent inflammation. On this account, one not unfrequently observes conjunctivitis, coryza, salivation, a feeling of suffocation, and slight bronchitis with cough in those who have inhaled bromine for therapeutic purposes, or accidentally, in rooms filled with the vapor.

The internal use of bromine-water also frequently causes coryza, lachrymation, bronchial catarrh, salivation, and diarrhœa. In the experiments of Glover<sup>1</sup> upon himself with this agent, there appeared only occasionally pains in the stomach, and, after larger doses, nausea, hiccough, burning in the mouth, oppression over the stomach, etc. Experiments of other authors showed that bromine-water used in small quantities for a short time, exerts a depressing influence upon the central nervous system. Those who took it experienced a feeling as if ants were crawling

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<sup>1</sup> Glover, *Edinb. Med. and Surg. Journ.*, 1842, p. 120.

over the skin, drowsiness, apathy, confusion of ideas, and weakness of the power of thought and memory. These symptoms disappeared immediately after stopping the drug.

#### POTASSII BROMIDUM.

In strong contrast with those affections, insignificant in number and intensity, which may develop after the use of bromine, are a number of incidental effects, produced by the internal administration of bromine salts, particularly the bromide of potassium (and what is true of this, applies also to the bromides of sodium and ammonium). They present, on the whole, a certain resemblance to the symptoms produced by the use of the iodide of potassium, but are not of so manifold a nature, and persist, as a rule, for a longer time. The mucous membranes are very frequently affected, but in a lesser degree than by iodide of potassium, while, on the other hand, in many cases, the influence upon the skin, and to a still greater extent upon the central nervous system, far exceeds in intensity and duration that of iodine.

The fact mentioned in discussing iodide of potassium, that the individuality of the affected person is of vital importance in determining the occurrence of incidental effects, applies also to bromide of potassium. For, while they show themselves in some persons after one or more small doses, others manifest a certain tolerance for even toxic quantities of the agent. In favor of the existence of this want of susceptibility, speaks, among others, in a characteristic manner, a case reported by Schweig<sup>1</sup> of a patient who manifested no reaction after taking thirty-one grams (℥ i.) of bromide of potassium in seven hours, and after ninety-three grams (℥ iiij.) in forty-eight hours, experienced only a diminution in the amount of urine excreted, with saliva-

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<sup>1</sup> Schweig, Virchow-Hirsch's Jahresber, 1876, p. 401.



tion and somnolence. Arthaud also states that, in fourteen cases in which he prescribed doses of from ten to twelve grams (3 iiss. to 3 iij.) daily, he never saw any affection of the skin.

Bromide of potassium produces, a short time after it is taken, a salty; according to others, a bitter after-taste in the mouth, and sometimes an increased flow of saliva, due to irritation of the buccal mucous membrane and a reflex hypersecretion from the salivary glands. In sensitive persons, there also occur burning in the throat, sometimes slight nausea, eructation, and, when it is taken upon an empty stomach, pains in the epigastric region, or a sensation of oppression, or warmth and fulness. A genuine catarrh of the stomach is a rarity, if the drug is not habitually taken in an improper manner, upon an empty stomach. One now and then observes eructation and vomiting, and more rarely diarrhœa, in some patients a short time after taking bromide of potassium. On the other hand, as Hütte<sup>1</sup> first showed, there occur, after long-continued small doses, or after larger quantities taken for a short time only, a blunting of the sensibility as well as the reflex action of the soft palate, the root of the tongue, the uvula, and the posterior wall of the pharynx. Gatumeau,<sup>2</sup> after three grams (gr. xlv.) of the drug had been taken, observed a complete analgesia of the pharynx and epiglottis, so that touching the posterior wall of the throat excited no reflex movements of swallowing. Krosz<sup>3</sup> also observed in his own person, after large doses of the bromide of potassium, such a lessening of the reflex excitability of the parts mentioned that no reflex nausea could be produced by irritating the velum. No less a diminution of sensibility is also experienced by the respiratory mucous membrane.

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<sup>1</sup> Hütte, *Gazette médicale de Paris*, 1850, Juin 28.

<sup>2</sup> Gatumeau: *Thèse*, Montpellier, 1869.

<sup>3</sup> Krosz, *Arch. f. exper. Pathologie u. Pharmacol.*, Bd. vi., p. 15.

This fact, in connection with the not-uncommonly observed appearance of bronchial catarrh with copious secretion, after the use of bromide of potassium, must not be lost sight of during the prolonged treatment of patients with this agent, particularly epileptics, maniacs, etc. Stillé<sup>1</sup> called attention to the fact that the catarrhs of the air-passages, which occur during treatment with bromide of potassium, may threaten life, if the use of the agent be continued, in consequence of the fact that the diminution of the reflex excitability of the respiratory mucous membrane prevents the occurrence of fits of coughing, which might remove the collected mucus. The bronchial catarrh is sometimes attended, as Höring<sup>2</sup> found in his own case, with pain in the larynx, paroxysms of coughing, and hoarseness of voice. According to older authorities, hæmoptysis also occurs in a large number of patients who use this drug, and disappears after its use is abandoned. No confirmation of this statement is, however, to be found in modern literature. Another accessory symptom of the already described effects of bromide of potassium which is often noticed, is a fœtid odor of the expired air, which Veiel<sup>3</sup> has recently called attention to. This cannot be due to pathological changes in the mouth, such as occur, for instance, after the use of mercury, for bromide of potassium produces but insignificant alterations in this locality. It is probable that the bromine is temporarily separated from the potassium in the body, and that the elimination of a portion of it by the lungs is the cause of the bad odor of the breath. This explanation is not intended to convey the idea that the bromine, as such, produces the catarrhal changes in the mucous membranes, for even if a small part

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<sup>1</sup> Stillé, Virchow-Hirsch's Jahresber., 1878, i., p. 384.

<sup>2</sup> Höring: Ueber die Wirkung des Broms und seiner Präparate auf den thierischen Organismus. Tübingen, 1838.

<sup>3</sup> Veiel, Vierteljahrsh. f. Dermatol. u. Syphil., 1875, p. 17.

of it does leave the body in the form of a vapor, the greater part, immediately after its separation from the potassium, finds enough of the alkaline metallic salts in the blood to be enabled to act upon the different mucous membranes in its original character of a bromine salt.

The mucous membranes of the nose and eyes may also be attacked, as is shown by the occasional occurrence of coryza, conjunctivitis, lachrymation, etc., after the use of bromide of potassium. Dilatation of the pupil is almost always noticed after repeated doses. Laborde<sup>1</sup> witnessed the occurrence, one or two hours after taking it, of dimness of vision and in some cases anæsthesia of the scleral conjunctiva. Hütte (l. c.) stated that myopia, amblyopia and diplopia could be produced by bromide of potassium. This was also believed by Martin Damourette and Pelvet,<sup>2</sup> while Nicol and Mossop claim to have observed dilatation of the retinal vessels after its use. These statements are opposed to the experiments of Krosz<sup>3</sup> upon himself and others, which always gave negative results as regards these pathological phenomena.

It has been demonstrated that the urino-genital apparatus is affected in an extensive degree by this drug. In addition to a real increase in the quantity of urine excreted, there sometimes occurs, in certain persons, strangury, a constant feeling of fulness of the bladder, and also a diminution of the sensibility of the urethral and vaginal mucous membranes. The sexual appetite, as Rabuteau<sup>4</sup> stated, is diminished by the long-continued use of the bromide of potassium. This effect of the drug had previously been utilized by Thielmann,<sup>5</sup> who prescribed it

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<sup>1</sup> Laborde, *Gazette médicale de Paris*, 1869.

<sup>2</sup> M. Damourette et Pelvet, *Bullet. de Thérap.*, lxxiii., 1867, p. 241.

<sup>3</sup> Krosz, l. c., p. 21.

<sup>4</sup> Rabuteau: *Gazette médicale de Paris*, 1869, p. 312.

<sup>5</sup> Thielmann, *Medic. Zeitung f. Russland*, 1854.

in doses of 0.18 gram (gr. iij.) as an antaphrodisiac. On the other hand, after one large dose, Laborde (l. c.) observed in himself, sexual excitement, erections and pollutions. Voisin<sup>1</sup> reports the same result as occurring after ordinary doses, but very rarely. Sometimes a diminution of the catamenial flow occurs in women.

The irritating effect which bromide of potassium is capable of producing upon the skin deprived of epidermis, as well as upon mucous membranes, is also manifested in a large number of cases after the internal administration of the agent, by the production of eruptions of various kinds. Their existence has been recognized for a long time, and they are usually collectively designated as "bromine acne," although they occupy a different place in the dermatological system.

Béranguier<sup>2</sup> observed the eruptions in fifty-three per cent, Clark and Amory<sup>3</sup> in sixty-six per cent, and Voisin in seventy-five per cent of all patients treated with bromide of potassium. Some authors, as Bedford Brown,<sup>4</sup> witnessed their occurrence attended with local or general elevation of temperature; while Veiel (l. c.) lays stress upon the fact that the acne-like eruption develops very gradually, without fever. Voisin found this complication only once, in a case of general bromine acne. Falret<sup>5</sup> states that he has always found the eruption when four grams (3 i.) of the salt were taken, but it is certain that it may occur after much smaller doses. Children are, as a rule, less frequently attacked by it.

The eruptions produced by this agent are differently described by different authors. They are, however, in

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<sup>1</sup> Voisin, *Bulletin générale de Thérapeut*, lxxxiii, 1867, p. 241.

<sup>2</sup> Béranguier, *Des éruptions provoquées par l'ingestion des médicaments*, Paris, 1874, p. 14.

<sup>3</sup> Clark and Amory, *Virchow-Hirsch's Jahresber.*, 1872.

<sup>4</sup> Bedford Brown, *Virchow-Hirsch's Jahresb.*, 1873, p. 358.

<sup>5</sup> Falret, *Annales Médico-psychologiques*, 1871.

great part due to affections of the sebaceous glands and their consequences, and since the different stages of development are usually represented at the same time in one individual, they closely simulate various dermatoses. Voisin (l. c.) has given a classification of all the skin-affections which occur after the use of bromide of potassium. In view of more recent observations by other authors, however, his classification may be advantageously increased by the addition of a few varieties, so that the following arrangement may be regarded as comprising all the changes of the skin which may be produced by bromide of potassium.

There appear, therefore, in certain individuals, according to their specific disposition, independently of sex and previous condition of health, at different periods during the administration of this drug, and under the widest variation as regards dose, various affections of the skin, such as:

1. *The erythematous form*.—This was observed by Veiel (l. c.) as the sole symptom produced by the drug, attended with fever, and diffusely spread over the lower extremities. The erythema caused the patient great pain. Brown (l. c.) also describes this eruption as an effect of bromide of potassium. In children he witnessed the occurrence of roseola under the same circumstances.

2. *Acne*.—This is by far the most frequent form of bromide of potassium eruption. According to Veiel a thickened skin, having a greasy look from the free secretion of sebaceous matter, as well as the presence of comedones or a pre-existing acne, especially predispose to the occurrence of this eruption. It appears under different modifications which, as regards their seat and their external behavior, present a complete analogy to ordinary acne. The first step in its formation is usually an erythematous condition of the skin of varying extent, attended with pricking and



burning. In this disease also, it is advantageous to distinguish two varieties, *acne punctata*, and *acne pustulosa*.

*a. Acne punctata*.—This usually precedes the pustular form. There appear red elevations, of barley-corn to pea size, on a more or less indurated base, surrounded by an areola, seated by preference on the face, the eyebrows, the hairy scalp, more rarely on the breast and back, and almost never on the lower extremities. Veiel found that the majority of the nodules were perforated by hairs. After a longer or shorter duration, this form may disappear with desquamation, or develop into :

*b. Acne pustulosa*.—This may be regarded either as the result of disintegration of the papules or as an independent form of eruption. The pustules are at first of pin-head size, of a yellowish-white color, and surrounded by an areola. They afterwards increase in size, and in rare cases, according to Voisin, may present the aspect of ecthyma-pustules. After a few days or weeks, the pustule empties out its contents and a firm nodule or a red spot remains behind. The number of the pustules varies greatly, the whole face being sometimes covered and disfigured by them. They may remain for days, or one or more months, and if the use of the drug be not stopped, even several years; but they usually disappear in from one to three weeks after the discontinuance of the bromide. Voisin (l. c.) also noticed that the number of the pustules increased or diminished with the increase or diminution of the dose. After healing, they often leave depressed, irregularly-rounded scars or spots behind. They form on the same locations as the nodules previously described, and become confluent in some cases, being usually covered with scabs on the scalp. Veiel sought in vain for bromine in the contents of the acne pustules, but could find it only in the urine. Guttman,<sup>1</sup> in the case of a man who, after using

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<sup>1</sup> Guttman, Virchow's Archiv, Bd 74, p 540.

for one year, at first four grams (3 i.), later twelve grams (3 iij.) of the bromide of potassium daily, developed a pustular acne, succeeded in demonstrating the presence of bromine in the pustules by the usual method, viz., separating the bromine from the potassium by the addition of chlorine water to the diluted and filtered pus, and extracting the bromine by chloroform.

3. *The urticaria-like form* was observed a few times by Veiel. Wheal-like elevations, varying in size from one-quarter to one-half an inch, showed themselves on erythematous portions of skin. They were exceedingly sensitive to touch, and gradually assumed a wart-like appearance, and took on suppurative action. The ulcer thus formed became deeper, and had an unhealthy aspect, but disappeared as soon as the bromide was discontinued. This form is without doubt identical with the tumor-like variety described by Voisin, which consists, according to his description, in the appearance of oblong or rounded tumors or elevations of the skin, with hard bases, two to five centimetres (one and a half to two inches) in diameter, and of a rosy-red or cherry color. They show themselves only on the legs or calves, and are covered with small yellowish prominences which, on careful examination, are seen to be agminated acne-like pustules, which empty their contents in the form of a creamy mass, either spontaneously or when punctured. They are very painful when touched, and may be transformed, if the use of the drug is continued, into foul atonic ulcers, which last three or four months, but if the agent is stopped, disappear in a few days.

Neumann<sup>1</sup> observed the same affection. He proved that these tumors are produced by an inflammation of the glands of the skin, attended with an increase of their cellular elements and consecutive cell-growth in the cutis,

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<sup>1</sup> Neumann, Wiener medic. Wochenschr., 1873, p. 124.

with enlargement of the papillæ. During this process the hair-follicles are dilated, and appear either as long tubes or globular bodies, containing pus, epithelial cells, and masses of smegma.

4. *Erythema nodosum*.—In two cases out of ninety-six, treated for a long time with bromide of potassium, Voisin witnessed the appearance on the arms and legs, as well as on the body, of patches slightly elevated above the skin, of different forms, sometimes having smooth and sometimes irregular edges. They attained a size of four millimetres to six centimetres (one-fifth to two and a half inches), were of a pale-red color in the centre and cherry-red in the periphery. They formed and disappeared very quickly, and presented the shape, color, and hard base of erythema nodosum, but resembled urticaria in reappearing when rubbed.

Veiel states that he has seen such an erythema nodosum a few times, but only on the lower extremities. After large doses of bromide of potassium, Smith<sup>1</sup> also saw patches of the size of a half-dollar, somewhat elevated above the surface of the skin, of a bluish-red color, seated upon both arms. They bled readily, were indolent, and disappeared soon after the drug was discontinued.

5. *The vesicular form*.—Voisin saw in a single case, that of a patient who had taken bromide of potassium for more than a year, a moist eczema on the thighs. This observation stands alone in literature.

6. *The furuncular form*.—The coincidence of the use of bromide of potassium with the appearance of furuncles has been asserted by so many authors that there can be no doubt that the two things may stand in the relation of cause and effect. Voisin, Smith, and Neumann saw furuncles occur in widely varying numbers, on many different

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<sup>1</sup> Smith, Virchow-Hirsch's Jahresbericht, 1879, p. 384.

parts of the body. The latter observed them on the hairy portions of the face, and on the forehead and neck.

It should finally be mentioned that Veiel (l. c.) witnessed the appearance of numerous warts on the face and legs of a boy, a short time after beginning the use of bromide of potassium.

Various opinions prevail as to the manner in which the above-described changes in the skin are produced after the internal administration of the bromine salts. Thus Clarke and Amory regard bromine-acne as a tropho-neurosis, and not as an effect of the eliminated bromide of potassium, and Veiel, also, does not believe that it is due to an irritation of the sebaceous glands produced by the deposition of bromine in them, having failed to find it there. Martin, Damourette, and Pelvet, on the other hand, believe the cause of the affection to be the irritation produced upon the skin in consequence of the elimination of the salt by this channel. The demonstration by Guttmann of bromide of potassium in the contents of the pustules, elevates into a certainty the *a priori* already probable hypothesis, that, under certain circumstances, an elimination of the salt by the skin may take place. In this way, on the one hand, an analogy is established with the similar changes in the skin which are excited by the salts of iodine, and, on the other, the view is supported that it is the bromine in the bromide of potassium which causes the affection, and not the potassium, as has been claimed by various authors. This is rendered more probable by the fact that other bromine combinations exert a similar influence. Thus Gowers<sup>1</sup> showed that similar eruptions appear after the use of bromide of ammonium, and Stark<sup>2</sup> saw acne occur in seventy-five per cent of all cases of epilepsy treated with bromide of sodium, which lasted longer

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<sup>1</sup> Gowers, *Lancet*, 1878, p. 866.

<sup>2</sup> Stark, *Zeitschr. f. Psychiatrie*, xxxii., p. 148.

than that produced by bromide of potassium, and resulted much more frequently in suppuration. He never found affections of the skin after a similar administration of chlorate of potassium.

The main treatment of these disorders consists in the suspension of the drug. Gowers (l. c.) used Fowler's solution in the treatment of bromine-acne, and found that five drops daily sufficed to cause the pustules to disappear in two weeks. This result was largely imaginary, however, since experience teaches that recovery usually occurs in this time without treatment.

Distinct from the previously mentioned transitory incidental effects of bromide of potassium are a group of functional disturbances in the sphere of the central and peripheral nervous system, which may be associated with one of the affections already described, may persist after the use of the drug has been suspended, and may, indeed, cause permanent injury to the health of the affected person. These phenomena constitute the condition known as "bromism."

Voisin distinguishes a chronic and an acute bromism and a bromine-cachexia. Intense frontal headache is usually present in all forms of the affection (a symptom occasionally observed after the use of bromide of potassium, without the production of cachectic conditions), and bronchial catarrh and cough may also complicate the situation. Acute bromism may show itself suddenly, even when the drug has been well borne for years, and is marked by a staggering gait, mental apathy, a dull expression of the eyes, and somnolence, while the chronic form is characterized by a sallow color of the face, dryness of the mouth, and an unpleasant odor of the breath, emaciation, diarrhœa, failure to preserve the usual bodily carriage, and trembling of the hands, with weakness of the memory and loss of will-power. It may also find expression in symptoms affecting the cerebro-spinal system, such



as delirium, hallucinations, and motor and sensory disturbances. Bromine-cachexia, according to Voisin (l. c.), begins with loss of appetite, emaciation and somnolence, and the condition of weakness associated with it leads, if the use of the drug be continued, to the formation of carbuncles, or the occurrence of pneumonia, which may prove fatal.

Although this classification is open to the objection of being too dogmatic, the fact is nevertheless established that all the phenomena which have been described, in their most varied modifications, may be produced by the use of bromide of potassium. The question as to which of the component parts of this preparation is to be regarded as the cause of these peculiar effects, has, in this case also, been differently answered at different times. It may, however, be accepted as proven, that they are due to the combined action of the bromine and the potassium, for Stark has shown, by a series of careful observations, that patients treated with chlorate of potassium also suffer from certain symptoms pertaining to the cerebral sphere, such as confusion of ideas, diminution of the reflex excitability of the throat, uncertainty of motion, etc. Krosz (l. c.) regards the bromine as the sole cause of bromism, as far as this affects the cerebral and nervous elements, and the potassium as the cause of the anæmia and the motor disturbances.

The treatment of bromism should be directed to the discontinuance of the use of the drug, the furthering of its speedy elimination from the body, and the ordering of an appropriate diet. The physical powers of the patient should be strengthened, and change of climate recommended for the psychical lesions. The rapid elimination of the bromide is most readily effected through the kidneys, which are the regular channels for the elimination of the halogen salts, and diuretics are, therefore, indicated.

## POTASSII CHLORAS.

Jacobi<sup>1</sup> has recently called attention to the dangers which may attend the use of chlorate of potassium in too large doses, and has reported a number of cases in which dangerous transitory symptoms occurred, as well as fatal results. These observations were confirmed later by Marchand,<sup>2</sup> Baginsky,<sup>3</sup> Hofmeier,<sup>4</sup> and Wegscheider.<sup>5</sup> On the ground of these facts, Marchand, whose cases, as has been shown by Küster,<sup>6</sup> cannot all stand criticism as regards correctness of diagnosis, demands that chlorate of potassium should be entirely abandoned in practice, particularly among children. But, if all drugs which produce hurtful effects when given in unsuitable quantities, or which, when given in ordinary doses, occasionally act abnormally, were treated in this manner, the materia medica would soon be reduced to a minimum. Instead of being so ready to dispense entirely with a drug, it would be well to exactly determine the doses suitable for different ages, and to carefully study the physical conditions which may predispose to the occurrence of unpleasant effects.

Ever since Lacombe<sup>7</sup> published a case of the kind, the fact has been recognized that chlorate of potassium in too large doses may cause fatal poisoning. Isambert,<sup>8</sup> who used it for several days in increasing doses of from eight to twenty grams (3 ij. to 3 v.), afterwards observed a

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<sup>1</sup> Jacobi, Gerhardt's Handbuch der Kinderkrankh., ii., p. 764, and the Med. Record, 1879, iii., 112.

<sup>2</sup> Marchand, Virchow's Archiv, Bd. 77, p. 456.

<sup>3</sup> Baginsky, Arch. f. Kinderheilkunde, nach einem Vortrage vom 10. November, 1878.

<sup>4</sup> Hofmeier, Deutsche medicin. Wochensch., 1880, Nos. 38 and 39.

<sup>5</sup> Wegscheider, eod. loco, No. 40.

<sup>6</sup> Küster, Berlin. klin. Wochenschr., 1880, No. 40.

<sup>7</sup> Lacombe, Jour. de Médecine de Bruxelles, 1856.

<sup>8</sup> Isambert: Etudes chimiques, physiologiques et cliniques sur l'emploi thérapeutique du Chlor. de Potasse. Paris, 1856.

greenish color of the stools and an increased flow of urine, with a feeling of oppression and pain over the kidneys. Ten minutes after it was taken, he could find it in the urine, the elimination lasting one or two days.

The cases of poisoning reported by these authors present a number of analogous symptoms, equalling in danger those caused by the most active poisons. These are: obstinate choking and vomiting, icteric discoloration of the skin, pains in the stomach and over the kidneys, and occasionally epistaxis, and diminution in quantity and even suppression of urine, lasting from one day to a day and a half, hæmaturia and albuminuria. With these symptoms may be associated sleeplessness, a feeling of alternate cold and heat without demonstrable fever, a small rapid pulse, and violent hiccough, and death may occur in a comatose condition. In the case reported by Wegscheider, there appeared, on the seventh day after the poisoning, at first only on the arms and forehead, a few red, not elevated spots, of the size of a pea, which became momentarily somewhat paler under pressure, and spread in the course of the next three days over the whole body, becoming larger, and of a copper-red color.

These observations should be contrasted, however, with the fact that hitherto no case has been recorded in literature, in which the administration of chlorate of potassium in medicinal doses was followed by injurious incidental effects similar to those just described, with the exception of the digestive disturbances. As medicinal doses we regard those proposed by Falck,<sup>1</sup> 0.1–0.5 gram (gr. ij.–vii.) at once, or five grams (gr. lxxv.) daily, or those of Jacobi (l. c.), for a child of from one to three years of age, one to two grams (gr. xv.–xxx.) daily, and for adults six to eight grams (3 iss.–ij.).

Of course we leave out of consideration, in this connec-

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<sup>1</sup> Falck: Uebersicht der Normalgaben der Arzneimittel. Marburg, 1875, p. 10.

tion, those cases in which no positive opinion can be formed as to whether a pre-existing diphtheritis or the chlorate of potassium prescribed for it has caused the threatening symptoms, or the death. Whenever the doses exceed the usual limit, a number of incidental effects may be produced, such as Marchand describes in his second observation. A boy from three to four years of age, suffering from stomatitis, who took at least ten grams (3 iiss.) of chlorate of potassium in one day, was attacked by drowsiness, vomiting, diarrhœa, and delirium. He also suffered from epistaxis, and passed bloody albuminous urine, containing a granular brownish sediment. Recovery took place in fourteen days.

The treatment of such cases can be only symptomatic. Emptying the stomach of any of the poison which it may contain, quieting the vomiting by ice-pills, champagne, etc., the administration of demulcent drinks, in order to act upon the affected kidneys, constitute the therapeutic measures to be employed.

#### POTASSII CHLORIDUM.

The chloride of potassium, which Sander<sup>1</sup> considers of equal value with the bromide of potassium, is said by him to have the advantage over it of producing no incidental effects. Further investigations have not confirmed either statement. For Stark<sup>2</sup> found, as has already been stated, that chloride of potassium has no effect whatever upon epileptic attacks, and that, on the other hand, it may, in certain individuals, in medicinal doses, produce a series of hurtful incidental effects in the same way as bromide of potassium. These consisted of a mild degree of confusion of ideas, drowsiness, torpidity, pains in all the limbs, diminished power of motion, difficulty of speech, loss of

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<sup>1</sup> Sander, *Centralbl. f. d. medicin. Wissenschaften*, 1808, No. 52.

<sup>2</sup> Stark, *Zeitschrift f. Psychiatrie*, xxxii., p. 159.

appetite, and in one case also a complete suspension of the reflex excitability of the pharynx. While these symptoms lasted, the frequency of the pulse was much diminished.

#### POTASSII SULPHAS.

The external application of the alkaline sulphates, particularly the sulphate of potassium, in the form of ointments, lotions and baths, causes not infrequently, in certain persons especially predisposed thereto, an irritation of the skin whose intensity is in proportion to the quantity of the salt used.

According to Bazin<sup>1</sup> small, intensely painful, confluent vesicles are formed upon a reddened base, which become filled with a serous or purulent fluid, and are surrounded with an areola two or three times as large as their diameter. This affection disappears in a few days.

More serious symptoms may also be produced by the inunction of sulphate of potassium. Thus Bazin,<sup>1</sup> after four or five applications to the lumbar region of a solution of four grams (3 i.) of sulphate of potassium in thirty grams (fl. 3 i.) of water, witnessed the occurrence of a violent phlegmonous inflammation, with the formation of pustules and abscesses. Strange to say, the skin of the thighs and buttocks, upon which the remedy was applied in the same manner, was affected by the inflammation in only a slight degree.

#### EXCITANTS.

##### CAMPHORA.

Upon the mucous membrane of the mouth camphor produces a biting, later a burning taste, and a subsequent feeling of coldness extending down to the stomach. If it is held in the mouth for some time, there appear symp-

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<sup>1</sup> Bazin, *Leçons sur les affections cutanées artificielles*. Paris, 1862, p. 110.



toms of irritation of the mucous membrane, such as pain, swelling, etc. The power of the drug to cause pain is also exerted when it is applied to the surfaces of wounds.

The effects produced by the internal administration of camphor in medicinal doses, differ, as Jörg<sup>1</sup> discovered, according to the individuality of the person. While some persons experience no abnormal sensations after 0.3–0.5 gram (gr. v.–viiij.), in others there appear, even after doses of 0.03–0.06 gram (gr.  $\frac{1}{2}$ –i.), headache, dizziness, slight confusion of ideas, redness of the face, dryness of the mouth, and thirst.

The alcoholic solution of camphor is said to act more powerfully than the drug in substance. Purkinje<sup>2</sup> observed in himself, after doses of 0.5 gram (gr. viij.) a pleasant excitement and liveliness, similar to intoxication, a desire for active motion, and a slight pricking in the skin.

While these symptoms rapidly disappear, as a rule, without leaving any unpleasant after-effects, the phenomena which not unfrequently follow the administration of camphor per enema are more serious, last longer, and demand therapeutic interference. There occur vomiting of masses smelling of camphor, strangury, heat, clammy sweating (the sweat also smelling of the drug), increased frequency of the pulse, and a condition of psychical exaltation, which may result in delirium.

In such cases, enemata of senna and sulphate of sodium, sinapisms to the neck and body, cold applications to the head and cold douches, are indicated.

### MOSCHUS.

The statements concerning the incidental effects of musk are to a certain extent contradictory. After doses

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<sup>1</sup> Jörg: Materialien zu einer Arzneimittellehre. Jena, 1827, p. 230.

<sup>2</sup> Purkinje, Neue Breslauer Samml., 1829, I., p. 428.

of 0.06–0.25 gram (gr. i.–iv.), Jörg<sup>1</sup> observed, in those upon whom he experimented, slight headache, particularly in the frontal region, confusion of ideas, giddiness, and oppression in the orbital fossæ. As regards the digestive canal, Jörg himself, after 0.18 gram (gr. iij.) experienced oppression in the stomach, and eructation with a penetrating odor of musk, and other observers noticed burning and dryness in the throat. Trousseau and Pidoux,<sup>2</sup> on the other hand, after the same dose, felt only a peculiar sensation of warmth in the stomach and abdomen, which afterwards changed into a decided sensation of hunger. Some time later they experienced pains in the temples and occipital region, dizziness, and excitement of the sexual organs.

According to the observations of Mitscherlich,<sup>3</sup> vomiting without digestive disturbances occasionally occurs after small doses of musk. This is probably due to a subjective aversion to the drug. Diarrhœa has also been observed after its use.

#### RADIX VALERIANÆ.

The root of *valeriana officinalis*, by many regarded as inert, is capable, as shown by the experiments of Jörg (l. c.) of producing unpleasant symptoms in some individuals, even in small doses. This author sometimes observed the following symptoms, either alone or combined, after the administration of four to twelve grams (3 i. to 3 iij.) of an infusion of valerian root: tickling in the throat, eructation, nausea, headache, especially in the frontal and parietal regions, a feeling of constriction of the pharynx, rumbling in the abdomen, diarrhœa, colicky pains, and anorexia.

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<sup>1</sup> Jörg. l. c., p. 285.

<sup>2</sup> Trousseau et Pidoux: *Traité de Thérap.*, III. Edit., II., p. 193.

<sup>3</sup> Mitscherlich: *Lehrbuch der Arzneimittellehre*. Berlin, 1849, Bd. II., p. 369.

Barbier<sup>1</sup> witnessed the occurrence of hallucinations of sight in a person treated with this agent.

#### FLORES ARNICÆ. TINCTURA ARNICÆ.

In some persons, irrespective of the mode of employment, even small quantities of arnica may cause disagreeable accidents. Infusions of 0.3 to 1.0 : 120.0 grams of water (gr. iv.-xv.: fl. ℥ iv.) not infrequently produce burning and tickling in the throat and mouth, pains in the stomach and abdomen, eructation, and occasionally rectal tenesmus and diarrhœa. There also occur oppressive headache, a sensation of fulness, giddiness, and unquiet sleep.

Wilkinghoff<sup>2</sup> has recently shown that when arnica is kept for some time, its active principle may grow weaker and finally become inert. This fact explains the differences which have been observed in the action of the drug.

It seems that the symptoms detailed, affecting the primæ viæ, are due to a local irritant action of the drug, and that the nervous disturbances are of a reflex nature. This view is sustained by the fact that if the tincture of arnica is applied to the healthy human skin, there may appear, in accordance with the strength of the preparation, either itching and burning, and later redness of the affected parts, or miliary or pea-sized vesicles may develop upon a reddened base, or even well-formed bullæ. These changes are followed by corresponding general symptoms.

#### NARCOTICS.

##### OPIMUM.

In the case of no other medicinal agent are the individual relations of the patient so influential in determining

<sup>1</sup> Barbier: Matière médic., 1824, II., p. 83.

<sup>2</sup> Wilkinghoff: Medicin. Beiträge zur Kenntniss der Arnica montana. Inaug. Diss., Bonn, 1880.

the occurrence of an abnormal mode of action as in that of opium. Among the more important of these relations are the nature of the disease, the age and sex of the patient, and, according to Charvet,<sup>1</sup> even the climate in which he lives, and the race to which he belongs; in short, that peculiar ready susceptibility to the unusual action of a certain drug which is dependent upon definite physical considerations, and which, in a given case, is very difficult of detection.

As regards the age of the patient, it should be stated that, in the cases of many children, injurious, and sometimes even fatal incidental effects may very readily follow the administration of opium. A knowledge of this fact has, therefore, for a long time caused it to be held as an axiom, that opiates should be but sparingly used in the treatment of children. In recent times, however, this teaching of experience has been frequently ignored, the dangers said to result from the use of such agents being regarded as exaggerated, even if not absolutely destitute of foundation. Nevertheless, that this warning is well grounded, and that a cautious use of these agents is indicated in such cases, is proved by the large number of accidents of this nature found in literature, occurring after moderate, and even the very smallest doses. Sobotka,<sup>2</sup> among others, reports several cases in which serious symptoms of poisoning appeared after almost minimal doses of opium, and one case of death after the administration of a few dessert-spoonfuls of a mixture containing three drops of laudanum and fifteen grams (fl.  $\frac{3}{4}$  ss.) Syrup. Papaver. alb., diluted to one hundred and eighty grams (fl.  $\frac{3}{4}$  vi.). After still smaller doses, 0.0006 to 0.0003 gram (gr.  $\frac{1}{1000}$  to  $\frac{1}{2000}$ ), Edwards,<sup>3</sup> and also Smith,<sup>4</sup> saw fatal results occur.

<sup>1</sup> Charvet: Die Wirkung des Opiums auf die thier. Oekonomie. Leipzig, 1872.

<sup>2</sup> Sobotka, Journ. f. Kinderkrankh., Dec., 1845.

<sup>3</sup> Edwards, in Taylor: Die Gifte.

<sup>4</sup> Smith, Medical Times and Gaz., 1854, April 15th, p. 386.

A large number of similar observations has been collected by Taylor.<sup>1</sup>

In women also, in consequence of their greater susceptibility to irritation, abnormal effects are much more easily produced by opium than in men, *cæteris paribus*. Gastric disturbances and cerebral hyperæmia are also factors which may exercise a favoring influence upon the occurrence of incidental effects. But constitutional bodily conditions, above all other things, are capable of modifying the normal effects of opium, or of producing undesirable symptoms.

The incidental effects hitherto described may show themselves after any manner of using opium. They seem to occur most readily, however, after its administration per enema, for numerous observations have been reported of cases in which threatening symptoms, or even death, occurred after enemata containing very small quantities of opium. Whether, as Dupuytren believed, a more rapid and complete absorption of opium takes place in the intestines than in the stomach, and, therefore, a more intense action of the drug occurs, has not yet been experimentally determined.

The central nervous system is first to be considered among the points of attack of opium. There not unfrequently occur in some persons, even after doses of 0.015 to 0.05 gram (gr.  $\frac{1}{4}$ – $\frac{3}{4}$ ), a feeling of excessive fulness of the head, dizziness, and headache, lasting several hours or even a number of days, seated sometimes in the frontal and sometimes in the occipital region. These symptoms were known to physicians of antiquity, such as Scribonius Largus and others. Tralles,<sup>2</sup> who reported such an observation upon a man, says in not very classical Latin: . . . *per multos dies ponderosissimum caput circumgestasse.*"

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<sup>1</sup> Taylor: *Die Gifte*, übersetzt von Seydeler. Cöln, 1863, Bd. iii, p. 31.

<sup>2</sup> Tralles: *Usus opii salubris et noxius*, Vratislav., 1774.



Convulsions are also said to have been produced by medicinal doses of opium. After larger doses, but still less than the maximum, there have been noticed buzzing and ringing in the ears, confusion of ideas, dimness of vision, disturbances of hearing, and partial or complete unconsciousness. The motor sphere may also be affected, there occurring in some cases, as Albers<sup>1</sup> stated, spasm of tendons, particularly of the extensor muscles, tremor of the hands, jerking, weakness, and even temporary paralysis, of the legs. Disturbances in the digestive apparatus may also appear, either simultaneously with these symptoms or as independent effects of the action of opium. The mouth and throat become dry, nausea and vomiting occur, and the appetite is lost. The latter, however, occurs in many cases only after repeated doses of the drug.

The changes which sometimes occur in the skin, after the use of opium, are especially worthy of study. Aside from the sometimes very profuse sweating which takes place, the face is congested, intensely reddened, and the rest of the skin feels hot to the touch. Annoying itching, without eruption, may also be present. This "pruritus opii" was mentioned by Dioscorides,<sup>2</sup> Paulus Ægineta,<sup>3</sup> and also by authors of the last century, and described as a tormenting and unbearable affection.

In rare cases, an eruption, with or without pruritus, is noticed after the use of opium. The first recorded observations on this subject emanated from Tralles,<sup>4</sup> who believed that the eruption bore a certain relation to the sweating which appeared simultaneously with it. The presence of the latter symptom is, however, not essential to the production of the exanthema. Duclos<sup>5</sup> lays spe-

<sup>1</sup> Albers, Virchow's Archiv, Bd. 26, p. 225.

<sup>2</sup> Dioscorides: De noxiis venenis, Cap. xxiii. Venetiis, 1516, p. 124.

<sup>3</sup> Paulus Ægineta: Opera. Lugduni, 1551, lib. v., cap. xliii., p. 355.

<sup>4</sup> Tralles, l. c., p. 137 and 138.

<sup>5</sup> Duclos, Journ. de Médec., Septem., Novembre, 1846. Ref. in Schmidt's Jahrb., Bd. 64, 1849, p. 74.

cial stress upon the fact that this may occur without augmentation of the secretion of the skin.

The eruption produced by opium consists usually of small, red, isolated spots, resembling in form that of measles. According to an observation of Rieken,<sup>1</sup> these spots may spread diffusely over the whole body, and thus present the appearance of scarlatina. Even the mucous membrane of the mouth and throat, this author states, may be attacked by this "erythematous inflammation." He witnessed the occurrence of such an eruption on a man every time he took opium internally, and even after the employment of ointments and collyria containing it. According to Béranguier,<sup>2</sup> the erythematous spots show themselves shortly after taking the drug, on the face, neck, arms, and breast, and disappear without leaving traces of their presence behind. Behrend<sup>3</sup> has also recently studied an opium eruption. It appeared after taking a few powders containing 0.015 gram (gr.  $\frac{1}{4}$ ) of opium with 0.5 gram (gr. viij.) of sugar, accompanied with violent itching, on the chest from the clavicles to the lower end of the sternum, on the inner surfaces of both upper arms, the flexor surfaces of the forearms, and over the wrist-joints, spreading down the thighs, from the neighborhood of the adductors to the popliteal spaces, and the posterior and inner aspects of the legs, terminating at the ankle in a stripe of livid color, about three fingers in width. It appeared as a pale scarlatina-like redness, which spread diffusely over the surrounding healthy skin, and, on closer examination, was seen to be composed of papules of pin-head size, lying close together. Several days after the eruption had passed away, there occurred a fine branny

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<sup>1</sup> Rieken, Schmidt's Jahrbücher, Bd. cvii., p. 22.

<sup>2</sup> Béranguier: Des éruptions provoquées par l'ingestion des médicaments. Paris, 1874.

<sup>3</sup> Behrend, Berl. klin. Wochensch., 1879, p. 626.

desquamation of the epidermis. Brand<sup>1</sup> also observed an eruption which spread over the trunk and flexor surfaces of the body, was attended with intense itching and high fever, and presented the appearance of a diffuse redness, made up of innumerable small points. In this and a similar case, there appeared, after eight days, a desquamation in the form of flakes of various sizes, which lasted nearly ten days.

The mode of occurrence of this exanthema is probably the same as that of all other drug eruptions. In the present instance, also, we may regard a direct action of the drug upon the affected portions of skin, or upon its trophic nerves, as the cause of the disease. This view, at least, aids us in forming an opinion as to the ultimate cause of the affection, although we are still unable to explain why only certain persons, and only certain portions of the bodies of those persons, are attacked. Although Behrend (l. c.), in describing the case of disease already alluded to, states that the occurrence of the opium eruption in consequence of a possible elimination of the drug by the skin, or even as an effect of its presence in the vessels of this organ, is to be excluded "with absolute certainty," this assertion must be regarded as absolutely unproved, its only force lying in the positiveness with which it was made. His supposition, that eruptions from opium and other drugs occur in consequence of some mysterious change produced in the blood by these agents, leads to absolutely untenable hypotheses, and would, even if it were correct, be likewise ultimately dependent upon a local action of the "dyscrasic blood" upon the skin.

As regards the therapeutics of the incidental effects of opium, recovery occurs spontaneously, as a rule, on the stoppage of the drug. If threatening symptoms, such as sopor, etc., have occurred, external excitants, stimulants,

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<sup>1</sup> Brand. Berl. klin. Wochenschr., 1879, p. 718.

ice, cold baths, sinapisms, etc., should be employed. According to Da Costa,<sup>1</sup> bromide of potassium possesses the power of preventing the incidental effects of opium, particularly the fainting, headache, dizziness, and nausea, and also of lessening the itching of the skin, when taken in doses of two to three and a half grams (gr. xxx. to l.), a few hours before the opium.

### MORPHIA.

What has been said of opium applies in the main to its most active constituent, morphia, and its salts. After its use also, headache, stupor, and particularly nausea and vomiting are observed. Thus Billroth,<sup>2</sup> in the case of a lady who took small doses, 0.007 gram (gr.  $\frac{1}{3}$ ), and even 0.003 gram (gr.  $\frac{1}{23}$ ), saw such anxiety, nausea, and vomiting, that, although suffering intense pain, she refused to take the remedy again. Laborde attributes the vomiting to the bad quality of the morphia, which after a time becomes partially transformed into apomorphia. However, no careful chemical investigation of this subject has yet been made.

Wernick<sup>3</sup> has called attention to the occurrence of a paræsthesia of taste after the use of morphia, which, according to his observations, is especially liable to occur in patients much reduced in health, and in robust persons after prolonged inanition, and is probably due to a central irritation analogous to that set up by santonin. The affected persons, shortly after the injection, complain of an intensely bitter or sour taste in the mouth, which usually ends simultaneously with the cessation of the morphia action.

The incidental effect which morphia sometimes pro-

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<sup>1</sup> Da Costa, Virchow-Hirsch's Jahresb., 1871, i., p. 307.

<sup>2</sup> Billroth, Wiener medicin. Wochenschr., 1868, p. 763.

<sup>3</sup> Wernick, Archiv f. Psychiatrie, Bd. ii., p. 174.

duces on the eyes has been carefully described by v. Graefe.<sup>1</sup> There occurs, particularly in very irritable persons, a spasm of the accommodation, the result of the stimulating influence of the drug upon the ciliary muscle. The focal point approaches so near that the range of accommodation is much limited, and myopia therefore occurs. Sommerbrodt also observed spasm of the accommodation lasting only thirty seconds, after the injection of 0.01 gram (gr.  $\frac{1}{10}$ ) of morphia. The outlines of the faces and heads of persons standing around the bed seemed to the patient to suddenly run together, so that he was unable to recognize any one. Although, according to v. Graefe, this condition usually appears thirty to forty-five minutes after the injection, in this case it presented itself immediately after it.

The skin may also be affected by morphia, as is shown by the occurrence of itching and eruptions after its use. Thus Apolant<sup>2</sup> saw in the case of a man who took several times twelve to fifteen drops of a solution of *Morphiæ mur.*, 0.08 (gr.  $\frac{1}{12}$ ), in *Aquæ Amygdalar.*, 10.0 (fl. 3 iiss.), an urticaria-like eruption, which the patient, without knowing what he had taken, at once attributed to morphia, having already discovered that he was specially susceptible to its incidental effects. The eyelids were swollen, the whole face œdematous, and red, wheal-like prominences appeared on the hands and other parts of the body. After five days, desquamation set in, during which large, coherent pieces of epidermis could be pulled off.

A distinction should be made between the true incidental effects of morphia already mentioned, and the symptoms which frequently appear without their cause being clear, after the direct intra-venous injection of the drug, in consequence of the canula being accidentally

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<sup>1</sup> V. Graefe, *Archiv f. Ophthalmologie*, Bd. ix., 2, p. 62.

<sup>2</sup> Apolant, *Berl. k'in. Wochenschr.*, 1877, p. 361.



thrust into a vein. In such a case, there occur, as Chouppe<sup>1</sup> states, redness of the face, heaviness and a feeling of fulness of the head, increase in frequency of the pulse to 100, great anxiety, and cold sweating. These symptoms last but a few minutes, and can be prevented by withdrawing the canula a little after introducing it, and by making the injection only when no blood flows from its opening.

In this connection we shall consider that pathological condition produced by the habitual use of opium or morphia, which has been made the subject of such thorough study, and is so frequently discussed in modern literature.

#### OPIUM EATING AND THE MORPHINE HABIT.

The phenomena which manifest themselves after the prolonged use of opium in increasing doses, are analogous to those produced by the internal or subcutaneous employment of morphia. The quantities which can be taken for a long time without injury by some persons must be regarded as simply enormous, when we consider how little of the drug is necessary to produce dangerous or even fatal poisoning in a normal system, and the statements as to their amount would be received with incredulity, if we were not forced to accept them as absolutely proven. The tolerance for such otherwise certainly fatal doses is produced by habituation to the action of the poison, and can be established only by beginning with small doses, and gradually increasing them. The opinion is justifiable that, in this manner, those cell-groups, whose functions are usually only temporarily affected by opium, are deprived of their energy by the chemical or physical influence continually brought to bear on them, or, in other words, that they constantly require a fresh stimulus of

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<sup>1</sup> Chouppe, *Gazette hebdomad. de Médecine et de Chirurg.*, Mars, 1876, p. 162.

increasing strength, in order to manifest the same functional capacity as formerly, and, at the same time, are protected against the danger of a poisonous action of the drug causing the irritation. A point must, however, be finally reached, at which the quantity administered no longer suffices to excite or restrain the functions of certain organs, and when a still further increase of the dose causes such profound changes in the organ itself, or in others, by a reflex or sympathetic action, that the symptoms of poisoning and its consequences appear.

These affections may be developed by the frequent therapeutic employment of opium or morphia. The patient, who has learned to appreciate its power of relieving pain, has recourse to the drug whenever opportunity offers, even in insignificant bodily ailments, in order to relieve conditions for which another would hardly seek medical aid. Thus the first step is taken upon the road which leads unalterably to the vicious use of these narcotics. For when unpleasant bodily conditions which might furnish an occasion for their use are lacking, there appear at first psychical emotions, such as sorrow or care, and later slight mental disturbances, anger, vexation, etc., take their place (for opiates in suitable doses produce happy forgetfulness, lasting for hours, or an agreeable alienation of consciousness). When even these inducements are lacking, the constantly diminishing capacity for work, the neglect of social and family duties, as well as numerous other alterations of the emotional nature and the bodily functions, furnish an excuse for still further increasing the dose, until bodily and mental marasmus, or natural or violent death, puts an end to the wicked practice.

Before the more rapidly and powerfully acting morphia came into such extensive employment as at present, the above-described phases of the abuse of narcotic drugs

were observed, either singly or collectively, after the use of opium. Flemming<sup>1</sup> furnishes a striking description of the moral condition and the physical sufferings of opium eaters. He shows how a confession of their vice can be drawn from such persons only by strategy, that they are lost to every feeling of shame, and how social and family ties are loosened by this passion. In advanced degrees of this vice, there occur depression or excitement of spirits, childish impatience, incapacity for thought or inability to fix the attention upon a certain object, a want of sympathy for the affairs of daily life, clouding of the memory, and weakening of the power of judgment. At the same time, bodily disturbances appear, among others, inability to sleep, gnawing pains in the stomach, loss of appetite, a feeling of chilliness with sweating, and not infrequently derangements of the sexual activity.

The same symptoms are produced by morphia taken internally. In a case reported by Samter,<sup>2</sup> it was taken for three years, and during a period of three hundred and twenty days, in which the patient was constantly under careful observation, he consumed 79.5 grams ( $\bar{3}$  iiss.) of the agent. Eder<sup>3</sup> saw still larger doses taken. The patient observed by him took laudanum for six years, in increasing doses to thirty grams (fl.  $\bar{3}$  viiss.) daily, for eighteen months pure opium, at first one gram (gr. xv.), later as much as nine grams ( $\bar{3}$  ij. gr. xv.) daily, and for six months morphia, beginning with 0.4 gram (gr. vi.) and increasing to 2.6 grams ( $\bar{3}$  ij.) daily.

The introduction of the practice of injecting morphia subcutaneously, and the habit of intrusting the syringe to the control of the patient, his friends, or the nurse, has undoubtedly largely contributed to the spread of the mor-

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<sup>1</sup> Flemming, British Medic. Journal, Feb. 15th, 1868, p. 177.

<sup>2</sup> Samter, Deutsche Klinik, 1864, 16, 17.

<sup>3</sup> Eder, Oesterreichische Zeitschrift f. pr. Heilkunde, 1864, No. 33.

phine habit, although we have not yet gone so far as to justify us in saying with Bouchardat,<sup>1</sup> "que le morphinisme fait à Berlin de tels progrès qu'il y a des maisons de santé spéciales pour en recueillir les victimes."

Observations on this subject have greatly increased in number during the past few years. From America, Mattison<sup>2</sup> has called attention to the abuse of morphia which prevails in that country. In Germany, Lähr<sup>3</sup> and Fiedler<sup>4</sup> were the first to raise their voices against the spread of this vice and to attribute the blame for it, in part at least, to physicians. At the same time with Fiedler, L. Lewin<sup>5</sup> described a case of morphinism. More recently Levinstein<sup>6</sup> has treated this condition most exhaustively, basing his remarks upon a large number of observations, and after him Burkart<sup>7</sup> communicated his views upon the subject.

All cases present in an equal degree a gradual continuous decline of the psychical life, and also a series of bodily disturbances similar to those which we have described in connection with opium, and as incidental effects of morphia. As exceptional symptoms, there appear in some cases slight, transitory albuminuria or glycosuria, such as occurs in other conditions of chronic intoxication. The morphia habit should be regarded as such a condition, and we cannot share the opinion of those who are inclined to consider as diseases *sui generis*, either single groups of symptoms, or the sum of all the pathological phenomena which this condition presents. For it is plain that arsenicism,

<sup>1</sup> Bouchardat, *Annuaire de Thérapeut. de Matière médic.* Paris, 1879, p. 13.

<sup>2</sup> Mattison, *Schmidt's Jahrbücher*, 1875, No. i., p. 21.

<sup>3</sup> Lähr, *Zeitschr. f. Psychiatrie*, 1872, H. 3.

<sup>4</sup> Fiedler, *Deutsche Zeitschr. f. pr. Medicin*, 1874, No. 27.

<sup>5</sup> L. Lewin, *ead. loco*, 1874, No. 28.

<sup>6</sup> Levinstein, *Die Morphiumsucht*, Berlin, 1876, and *Berl. klin. Wochenschr.*, 1875, No. 48.

<sup>7</sup> Burkart, *Die chron. Morphinumvergiftung*, etc. Bonn, 1877.

alcoholism, the saturnine affections, and others, conditions in which the mental and bodily attributes are seriously and extensively disordered, can be regarded from a clinical stand-point only as intoxications, each of which has received a special stamp only because a series of secondary phenomena have rendered the pathological picture more complicated, in consequence of the long duration of the condition.

The treatment of opium-eating and the morphine-habit consists, of course, in the withholding of the particular drug. Opinions differ as to the manner in which this should be done, whether suddenly or gradually. The discussion of this question, as regards pure opium, was already carried on at a time when the morphine-habit was still unknown. Christison first practised the sudden withdrawal of the drug, in the year 1850. According to Flemming (l. c.), the mental and physical sufferings of the patient are much increased by this method of treatment. He becomes sleepless, irritable, anxious, despairing, and begs and prays for opium. With this condition are associated thirst, neuralgic pains, diarrhœa, sweating, attacks of chilliness, etc. But, on the other hand, the sudden stoppage of the drug puts the moral and physical powers of the patient to a less severe test than the method of gradual diminution of the quantity taken, in which the same unpleasant reaction takes place at every dose, no matter how small it may be. In recent times both methods have found defenders, as regards the morphine-habit also. During the course of the withdrawal, when the patient is completely isolated, and has no opportunity to procure the drug for himself, there frequently occur conditions of collapse, for counteracting which stimulants must be freely employed, since otherwise a fatal result may easily take place. Just as much to be dreaded are the conditions of excitement which appear soon after the



withdrawal of the morphia, in which attempts at suicide are by no means uncommon. To determine whether, during the withdrawal, morphia has been secretly administered, nothing can be done except to study the subjective condition of the patient. If this be very good, a suspicion that such is the case would be justifiable. The demonstration of the presence of the alkaloid in the urine generally fails, since it rapidly decomposes in the blood, as Landsberg<sup>1</sup> has shown.

Only a very insignificant minority of these patients succeed in really and permanently weaning themselves from the drug. The large majority fall back again into the old vicious habit sooner or later after the withdrawal. The employment of substitutes for morphia, such as *cannabis indica*, *hyoscyamus*, etc., is attended with no practical benefit. The use of atropia, valerianate of zinc, quinine, and bromide of potassium as symptomatic remedies is not indicated, because as long as the exciting cause is at work, the temporary relief of this or that pathological phenomenon is of no practical value.

#### CANNABIS INDICA.

In accordance with the good quality of the preparation and the individuality of the patient, unexpected results of varying intensity appear after the use of the preparations of hemp. Unlike the phenomena produced by the ingestion of opium, these are relatively rare and speedily pass away, leaving no unpleasant after-effects. A number of observations bearing upon this subject were communicated by Schroff.<sup>2</sup> He generally noticed in those upon whom he experimented, a blunting of the tactile sensibility, a feeling as if the lower extremities were asleep, dizziness, visual hallucinations, and slight delirium.

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<sup>1</sup> Landsberg, *Pflüger's Archiv*, Bd. xxiii., 1880, p. 432.

<sup>2</sup> v. Schroff: *Lehrbuch der Pharmakologie*, 1855, p. 536.

Husemann,<sup>1</sup> in experimenting upon himself, once produced a condition of tearful joyfulness, while, on another occasion, his mental condition was sorrowful—a state which was in exact correspondence with the hallucinations and illusions which he experienced at the time.

#### CAFFEÏNUM.

Caffeïn, which is so much used in the treatment of migraine, seems to produce different effects upon different persons. Husemann,<sup>2</sup> who took only 0.24 gram (gr. iv.), afterwards observed intense congestion of the head and difficulty of respiration; while Albers,<sup>3</sup> after 0.18–0.3 gram (gr. iij.–v.) of the citrate of caffeïn, felt no effects whatever; and Frerichs, even after two grams (3 ss.) of pure caffeïn, noticed only congestion of the head and one attack of vomiting.

#### FOLIA HYOSCYAMI—EXTR. HYOSCYAMI.

The incidental effects which show themselves after the use of preparations of henbane correspond in many respects to those produced by belladonna. The first, as regards importance, is an affection of the skin, which presents itself in many persons as an erythema. Thus, Cabot<sup>4</sup> describes the case of a man who took tincture of hyoscyamus to relieve pains in the abdomen. A short time afterwards, his nose began to swell, and gradually the whole body became similarly affected, and the seat of itching and burning. The face was red and shining, and the redness gradually spread as far as the umbilicus, below which there appeared only isolated red patches. This

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<sup>1</sup> Husemann: *Handbuch der Toxikologie*, 1862, p. 430.

<sup>2</sup> Husemann, l. c., p. 544.

<sup>3</sup> Albers, *Deutsche Klinik*, 1853, 34.

<sup>4</sup> Cabot, *Amer. Jour. of Med. Sciences*, Oct., 1851.

erythema began to grow paler an hour and a half later, and had entirely disappeared by the second day. Bessières,<sup>1</sup> in the case of a lady who was accustomed to use vaginal injections of a decoction of hyoscyamus, also observed an erythema on the face after she used the same preparation, per enema. Picard<sup>2</sup> also reports the case of a woman who, after an injection into the rectum of a medicinal dose of hyoscyamus, was attacked by an intense erythema of the face.

Golding<sup>3</sup> saw a pustular eruption several times after the repeated internal use of small doses of henbane.

Functional disturbances in other organs may appear simultaneously with this affection. In this category belong an excessive dilatation of the pupils, a feeling of dizziness, weakness, and collapse. Paralytic conditions of the upper and lower extremities have been also occasionally observed. If the use of the drug be persisted in, it is said that swelling of the parotids, salivation, and catarrhal inflammation of the nasal mucous membrane may also occur.

Therapeutical interference is necessary only on the appearance of symptoms of weakness, in which case stimulants should be administered.

### ATROPIA.

#### *Atropiæ Sulphas.*

During the external employment in ophthalmological practice of atropia in the ordinary doses, there appear in some persons, in addition to its physiological mydriatic effect, certain abnormal local and general symptoms, due to the absorption of the agent.

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<sup>1</sup> Bessières: Abeille médicale, Novembre, 1853.

<sup>2</sup> Picard, Ref. in Fodéré: Traité de Médec. légale et d'hygiène publ., T. iv., p. 25.

<sup>3</sup> Golding, in Wibmer: Wirkungen der Arzneimittel und Gifte. München, 1842, Bd iii, p. 1219.

As regards the local phenomena, v. Graefe<sup>1</sup> made the observation that the at first unirritating mydriatic could not be long borne by some individuals. "An anatomical change is produced, as a result of the repeated action of the agent, which modifies the normal susceptibility of the conjunctiva to further medicinal influences. When the membrane is once saturated with atropia, there therefore occurs, after each new instillation, blepharo-conjunctival irritation, lachrymation, œdema of the lids, and even eczematous eruptions. This antipathy of the conjunctiva to atropia sometimes persists for months after the suspension of its use, during which time the mucous membrane may present an entirely normal appearance. In the most pronounced cases, granulations of a peculiar kind appear, somewhat similar to the ordinary vesicular lymph-follicles of the lower lid, and only distinguishable from them by their somewhat more consistent and more yellowish contents, and the altered condition of the vascular supply of the mucous membrane." Graefe recommends, in order to be able to employ atropia again in such cases, the intermittent use of solutions of the acetate of lead or nitrate of silver.

In addition to these local changes, Graefe<sup>2</sup> sometimes noticed permanent dilatation of the pupils, after the use of atropia, particularly in cases of syphilitic iritis.

The symptoms due to absorption of the agent, which occur after its application to the eye, point to a central action of atropia, such as ordinarily occurs only in cases of poisoning by it. They are, as a rule, but rarely observed after instillation of atropia or the use of collyria containing it, and are not dependent upon the quantity of the drug absorbed by the eye, but are due to the action of that portion which is taken up by the lachrymal ducts, and

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<sup>1</sup> v. Graefe, *Archiv f. Ophthalmol.*, Bd. i., 2, p. 242, and Bd. x., 2, p. 200.

<sup>2</sup> v. Graefe, *eod. loco*, Bd. ii.

reaches the throat and stomach. Susceptibility to this mode of action of atropia stands, therefore, in direct proportion to the width of the tear-passages. Proof of this statement is furnished, according to R. Liebreich,<sup>1</sup> by those who have impermeable tear-ducts, whose general condition is never affected by even the largest doses, used for a long period. According to an observation of Chassaingnac, in a case of double cataract with adhesions of the iris to the capsule, in which three or four drops of a solution of atropia (0.06 gram to ten grams of water; gr. i.-fl. ʒ iiss.) were instilled into the eye, there occurred in thirty minutes dizziness, and later, turgescence of the face, tickling in the throat, and hallucinations of the senses. These symptoms disappeared spontaneously three or four days later. Laborde<sup>2</sup> saw fulness of the head and marked delirium occur after its use by adults, while Galezowski observed convulsive phenomena in children only.

This statement of Laborde finds interesting confirmation in an observation of Kowalewski.<sup>3</sup> After the application of a considerable quantity of atropia to the eye of a man, there appeared great excitement as well as hallucinations of hearing, sight, and feeling, which the patient described as the embodiment of abstract ideas. On the fifth day, dryness of the mouth, spasm of the throat, etc., also appeared, and complete recovery took place only after ten days.

Especially worthy of notice in this connection is an observation of v. Graefe,<sup>4</sup> that in consequence of the prolonged use of atropin collyria, there not infrequently occur symptoms which are recognizable as erethistic weakness and interruption of assimilation. It is difficult

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<sup>1</sup> R. Liebreich, Berl. klin. Wochenschr., 1864, p. 457.

<sup>2</sup> Laborde, Gazette médicale de Paris, 1878, p. 606.

<sup>3</sup> Kowalewski, Allgemeine Zeitsch. f. Psychiatrie, Bd. 36. Heft 4.

<sup>4</sup> v. Graefe, Archiv f. Ophthalmologie, Bd. ix., 1864.



to recognize this condition and refer it to its real cause, on account of the fact that other symptoms of the action of atropia are lacking.

It is unnecessary to attempt curative treatment of these affections, because the above-described symptoms usually cease soon after suspending the use of the drug. If they become very urgent, small doses of morphia should be administered (0.005–0.01 gram — gr.  $\frac{1}{12}$ – $\frac{1}{6}$ ). Prophylactic measures are, however, indicated. According to the advice of R. Liebreich (l. c.), patients should be recommended to bend the head forwards during instillation of atropia, not to swallow the tears or the fluid which drops from the eyes, to blow their noses frequently, and to gargle, or to press a finger into the corner of the eye and draw the tear-duct downwards. Since this manœuvre does not always succeed, when the patient is awkward or in a reclining position, Liebreich employs a small forceps similar to a *serre-fine*, with which the lid at the angle of the eye is grasped in such a manner as to produce a slight degree of ectropium, and turn the *puncta lachrymalia* downwards and outwards. It usually suffices to treat only the lower lid in this manner; when large doses are used, and in the cases of sensitive persons, the upper lid must also be included.

Incidental effects are more rarely observed after the internal administration of atropia. When they do appear, they are generally limited to dryness of the mouth, a feeling of rawness in the throat, slight fulness of the head, the appearance of rings before the eyes, and sometimes diplopia, and redness of the face. Only after large doses do threatening symptoms show themselves, on the part of the circulatory system, the motor and psychical spheres, and the general sensibility.

An affection of the skin is occasionally observed after

small medicinal doses. Thus Lusanna<sup>1</sup> reports a case, in which fifteen minutes after taking a small dose of atropia the skin became intensely red, and presented the appearance of having been exposed to the intense heat of the sun. This erythema lasted from one-half to one hour, and appeared every time the drug was taken.

## BELLADONNA.

*Folia—Radix—Extractum—Unguentum Belladonnæ.*

After the external or internal employment of belladonna, various authors have observed an exanthema, which, like most drug-eruptions, is of a very transitory nature. The affection is sometimes general and sometimes localized, and appears, as Guérard<sup>2</sup> states, especially in children, even after very small doses. It usually assumes the form of extensive erythematous patches, or a scarlatinous exanthema. The spots disappear on pressure, but return immediately when this is removed. They affect, by preference, the face and neck, and appear without itching, and speedily pass away. They may show themselves a very short time after the administration of the drug, and may pass through the various stages of development in a few hours. In some cases, as if to render perfect the apparent likeness to scarlatina, there follow redness and painful swelling of the throat. Fever is not present, and no desquamation occurs.

Traube<sup>3</sup> gives it as a result of his experience that such an eruption may occur after taking belladonna. Béranguier<sup>4</sup> observed a diffuse scarlatinous redness, which ap-

<sup>1</sup> Lusanna, L'Union médicale, 1854.

<sup>2</sup> Guérard: Des éruptions medicamenteuses pathogénétiques. Paris, 1862, p. 26.

<sup>3</sup> Traube: Beiträge zur Pathologie und Physiologie. Berlin, 1871, ii., Abth. 1, p. 163.

<sup>4</sup> Béranguier, l. c., p. 31.

peared after taking a mixture containing belladonna, lasted eight hours, and then suddenly disappeared. In the cases of two lying-in women, who had used for several days a belladonna liniment, to relieve swelling of the mammary glands, Wilson<sup>1</sup> witnessed the occurrence of a scarlatina-like exanthema, which disappeared without desquamation after three or four days. Köbner<sup>2</sup> also found well-marked hyperæmia, particularly of the face, after the introduction into the vagina of a suppository containing extract of belladonna.

It will be readily understood from what has been said about atropia, that belladonna, after its external or internal use, may also excite other abnormal somatic symptoms which are identical with the phenomena produced by the action of atropia. Two cases reported by Golden<sup>3</sup> are worthy of notice, in which the inunction of belladonna ointment upon the breast suppressed the secretion of milk.

#### DUBOISINUM.

Duboisia is the yellow alkaloid, in the form of an extract, prepared by Gerrard, and at the same time by Petit (1878) from a plant which grows in Australia, the *Duboisia myoporoides*, belonging to the family of Solanaceæ. It is sparingly soluble in water (1 : 120) but dissolves readily in alcohol, chloroform, etc. The watery solution has a slightly alkaline reaction. Its sulphuric acid compound is crystalline.

The main effect of duboisia is to produce dilatation of the pupils, in which respect it equals atropia, or even far surpasses it, as some investigators found. Wecker<sup>4</sup> states that it is less irritating to the conjunctiva than atropia. A

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<sup>1</sup> Wilson, Virchow-Hirsch's Jahresbericht f. d. ges. Medicin, 1872, i., p. 380.

<sup>2</sup> Köbner, Berl. klin. Wochenschr., 1877, p. 328.

<sup>3</sup> Golden, Lancet, 1856, No. 6.

<sup>4</sup> Wecker, Bulletin de Thérapeutique, 1879.

solution of 0.001 gram (gr.  $\frac{1}{60}$ ) in water, subcutaneously injected, prevents or lessens the colliquative night-sweats of phthisical patients.

Gubler, on the other hand, after the subcutaneous injection of 0.0005 gram (gr.  $\frac{1}{120}$ ) of this substance, observed dryness of the throat and visual disturbances, and after 0.001 gram (gr.  $\frac{1}{60}$ ), thirst, increased frequency of the pulse, redness of the skin, and sometimes collapse. Sidney Ringer found that three drops of a solution of duboisia 1:4 parts of water, subcutaneously injected at the height of the action of pilocarpin, made the skin perfectly dry in seven minutes, and after ten minutes produced such a sensation of dryness in the mouth that the patient complained of it.

Incidental effects have already been observed after the external application of this drug to the eye also. Thus Davidson<sup>1</sup> reports eight cases, in which, after the instillation of duboisia into the conjunctival sac, pathological symptoms of varying intensity appeared, such as dizziness, restlessness, and excitement increasing to violent delirium. Dryness of the throat was also observed in some cases. Schöler<sup>2</sup> used the sulphate in a solution of 0.05:5.0 (gr.  $\frac{3}{4}$ : lxxv.) without producing symptoms of general intoxication. On the other hand, in three or four cases, after the employment of this agent, he observed a well-marked conjunctivitis follicularis, and in two or three cases pain during the instillation, redness of the conjunctiva, and failure of the effect upon the pupils.

#### ACONITIA.

##### *Tubera—Extract.—Tinct. Aconiti.*

The effects of the different kinds of aconitia prove that the mode of preparation of the alkaloids is capable of

<sup>1</sup> Davidson, Lancet, September 6th, 1879.

<sup>2</sup> Schöler, Jahresbericht über s. Augenklinik für 1878. Berlin, 1879.

modifying their action. While German aconitia is by no means to be regarded as relatively one of the most poisonous of substances, this claim is made by nearly all English experimenters for English aconitia (Morson's napelline or pure aconitine) which is probably prepared by a secret process from *Aconitum ferox*.

While the largest permissible dose of German aconitia, according to the *Pharmacopœa Germanica*, is 0.004 gram, (gr.  $\frac{1}{16}$ ), Pereira<sup>1</sup> saw almost fatal consequences ensue from the use of 0.0015 gram (gr.  $\frac{1}{60}$ ) of English aconitia. Although it is true that the individuality of the persons using these powerful agents plays a certain rôle, the differences in the mode of action of the two kinds of aconitia, which have been demonstrated by Schroff also, are too great to be left out of consideration by physicians in their observations of the injurious incidental effects of the drug, such as have been observed in different degrees after both preparations.

According to Pereira, English aconitia, even in very small doses, produces a sensation of heat and itching on the surface of the body. After its external employment, Turnbull<sup>2</sup> observed pricking of the parts to which it was applied, and Schroff,<sup>3</sup> after painting a weak alcoholic solution of this aconitia upon the forearm, experienced pricking and formication, without the appearance of inflammatory changes.

Cases of poisoning, which occurred in consequence of the administration of English instead of German aconitia, are frequently met with in literature. The English preparation should, in our opinion, be entirely abandoned for internal use.

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<sup>1</sup> Pereira, Refer. in Husemann, *Pflanzenstoffe*, 1871, p. 226.

<sup>2</sup> Turnbull, Refer. in Husemann, *Pflanzenstoffe*, 1871, p. 226.

<sup>3</sup> Schroff, *Jour. f. Pharmakodynamik, Toxikologie und Therapie*, Bd. i., 1857, p. 365.



German aconitia and the other pharmaceutical preparations made from the Wolfsbane, cause, as Dworzak and Heinrich<sup>1</sup> found in their own cases, a biting, burning feeling upon the lips and tongue, and salivation. An eruption of white vesicles has also been occasionally observed on these parts. A vague drawing sensation in the face also occurs not infrequently, which may pass into a persistent pain involving the distribution of the trigeminal nerve, and be accompanied by an intensely annoying feeling of pricking, usually on the chin and cheeks, but also appearing on the body and extremities. The gastric and intestinal mucous membranes are also irritated by this drug. Nausea occurs, and even vomiting and rumbling in the abdomen. If the use of the aconite be continued, more remote effects are produced, such as headaches, more or less intense fulness of the head, buzzing in the ears, and general weakness, symptoms which disappear a short time after the administration of the agent is suspended.

Although as a rule no symptoms which threaten life are to be expected from the use of medicinal doses of German and other preparations of aconitia, direct therapeutical interference may become necessary when cardiac lesions or other causes predisposing to a more intense action of the drug are present. Contrary to the view formerly entertained, it has been shown by L. Lewin<sup>2</sup> that aconitia belongs to that class of cardiac poisons whose fatal action may be long deferred, or even absolutely prevented, by long-continued artificial respiration. This procedure must therefore be resorted to whenever symptoms of dyspnoea and anomalous heart-action (interruption and irregularity of rhythm) show themselves. When milder effects of aconitia appear, the usual stimulants and diuretics may

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<sup>1</sup> Dworzak u. Heinrich, *Prager Vierteljahr.*, Bd. 42, p. 153, et seq

<sup>2</sup> L. Lewin: *Experimentelle Untersuchungen über die Wirkung d. Aconitin auf d. Herz.* Berlin, 1870.

also be employed to produce a more rapid elimination of the drug. No direct antidote for aconitia is known.

#### VERATRIA.

##### *Rhizoma—Tinct. Veratri.*

The alkaloid prepared from white hellebore as well as the roots of the plant produce not infrequently, when used therapeutically, a few pathological phenomena which were known even to physicians of the middle ages. They may occur with more or less intensity after any mode of administration of the drug.

A mere trace of the powder, accidentally brought in contact with the nasal mucous membrane, causes violent sneezing lasting for a considerable period, which may result in profuse epistaxis. The conjunctiva is affected with equal violence when veratria in solution or in the form of an ointment is applied to it. The relatively extensive external use of this agent in the treatment of neuralgias of various nerve-tracts has furnished abundant opportunity for becoming familiar with the symptoms which it produces. An ointment of 0.6–1.0 gram (gr. x.–xv.) of veratria, thirty grams (ȝ i.) of simple cerate, soon produces prickling and a feeling of increased heat, not only at the point of application, but also on remote parts of the body. This sensation, according to Reiche,<sup>1</sup> gradually increases to burning, and if the application be long continued, a feeling of restlessness and anxiety appears. These phenomena may become permanent, if the use of the drug be not discontinued, and deprive the patient of sleep. An itching petechial or vesicular eruption, which soon disappears after the use of the drug is stopped, is occasionally observed on different parts of the body.

More intense incidental effects may be produced by the

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<sup>1</sup> Reiche, Medic. Zeitung d. Vereins f. Heilkunde, 1839, 23.

internal use of the drug. Owing to its power of reducing the frequency of the pulse, the blood-pressure and the temperature, and of slowing the respiration, veratria was and is still employed in acute febrile affections, particularly in pneumonia. In such cases, it is usually administered several times daily, in doses of from 0.003–0.0005 gram (gr.  $\frac{1}{200}$ – $\frac{1}{400}$ ), and even beyond the maximal limit of 0.01 gram (gr.  $\frac{1}{10}$ ). But even the small normal doses usually excite dryness in the mouth, burning thirst, difficulty in swallowing, nausea, choking, and vomiting, and sometimes also salivation, colicky pains, and diarrhoea, in which the stools may be tinged with blood. Children often vomit, as Forcke<sup>1</sup> states, even after the first dose, adults more rarely.

During the prolonged use of medicinal doses of the drug, there occurs a pricking or burning feeling on remote parts of the body, particularly the extremities. In some individuals there appear dizziness and dimness of sight, and also trembling and unsteadiness of gait. In others, well-marked collapse may take place. Cerebral symptoms occur not infrequently in children after the administration of tincture of *veratrum viride*. Thus, Fleischmann<sup>2</sup> reports that, after the hourly administration to a boy of a teaspoonful of the following mixture: Tinct. Veratri virid. gtt. vi., Mucilag. acac. 60 grams (fl.  $\frac{3}{4}$  ij.), there appeared dryness of the throat, great thirst, and, after a while, convulsive movements of the hands and fingers lasting but a short time, foolish talking, and mild delirium.

Forcke, in a few cases, saw a pustular eruption on the face, most marked around the mouth.

After the subcutaneous injection of the drug in alcoholic

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<sup>1</sup> Forcke: Physiologisch-therapeutische Untersuchungen über d. Veratrin. Hannover, 1837.

<sup>2</sup> Fleischmann, Prager medic. Wochenschr., 1876, No. 10.

solution, in doses of 0.0012–0.0015 gram (gr.  $\frac{1}{65}$ – $\frac{1}{60}$ ), Eulenburg<sup>1</sup> witnessed the formation of an abscess in one case, and usually the appearance around the point of puncture of a slight, sometimes spotted, redness and swelling. The feeling of burning lasted several hours after the injection. Hiffelsheim also noticed pain and erythema after the hypodermic use of veratria. Sometimes the toxic action was so much intensified as to lead to prostration.

The treatment of these incidental effects, besides the immediate suspension of the use of the drug, should consist in the administration of analeptic substances, particularly the aromatic spirits of ammonia, in twenty to sixty drop doses,<sup>2</sup> or, according to Reiche, of black coffee with lemon juice. In cases where gastric catarrh is present, the drug, according to Tröttscher,<sup>3</sup> should never be prescribed.

#### EXTRACTUM FABÆ CALABARICÆ.

##### *Eserina s. Physostigmia.*

The incidental effects which show themselves after the application of preparations of Calabar bean to the eye have been clearly described in the classical investigations of A. v. Graefe.<sup>4</sup> According to this author, the drug passes through the cornea, is dissolved in the fluids of the eye, and acts directly upon the iris and ciliary muscle. He found that immediately after the instillation of a solution of the alcoholic extract in glycerin, there appeared an itching feeling in the conjunctival sac, with a corresponding reflex action upon the orbicularis muscle and the lachrymal secretion, varying in degree with the individuality of the patient and the concentration of the preparation employed. Afterwards, when the contraction of

<sup>1</sup> Eulenburg: Die hypodermatischen Injectionen. Berlin, 1875, p. 278.

<sup>2</sup> Husemann: Pflanzenstoffe. Berlin, 1871, p. 510.

<sup>3</sup> Tröttscher: Wiener Medicin. Halle, 1863, p. 487.

<sup>4</sup> A. v. Graefe, Archiv f. Ophthalmologie, Bd. ix., 1863, III., p. 87.

the pupil and the accommodative changes begin, the subjects of experiment complain of a painful tense sensation, partly along the equator of the globe, and partly in front of it, in the region of the ciliary body. Other observers describe a nervous aching pain in the whole globe, which may, after the manner of ciliary neuroses, spread along the supraorbital nerves, and, like migraine, may extend over the corresponding side of the head. Graefe leaves it undecided whether spasm of the tensor or of the sphincter is more involved in the production of these pains.

He failed to observe any more remote effects. If such should appear, they would be most easily explained by the passage of the drug along the tear-ducts.

After the administration of small doses of the extract of Calabar bean, as it is sometimes employed in the treatment of neuralgias, tetanus, and epilepsy, and also in cases of poisoning by atropia and strychnia, Fraser<sup>1</sup> noticed a painful feeling in the epigastrium, as well as giddiness and weakness of the muscles of the extremities. The last symptom may pass into a condition resembling paralysis, which, however, lasts but a short time.

After small doses of physostigmia, Leven<sup>2</sup> witnessed the occurrence of nausea and general discomfort.

#### AMYGDALÆ AMARÆ.

##### *Aqua Amygdal. Amararum—Aqua Laurocerasi.*

Stillé<sup>3</sup> states that bitter almonds, in medicinal doses, sometimes produce an abundant eruption resembling urticaria. Gregory also noticed such an eruption upon himself after eating a bitter almond. This effect is due to the presence of hydrocyanic acid in the almond, as is proven

<sup>1</sup> Fraser: Transactions of the Royal Society of Edinburgh, xxiv., 1867, 73.

<sup>2</sup> Leven, Jour. de Pharmac. et Chimie, I., 70.

<sup>3</sup> Stillé; Therapeutics and Materia Medica. Philadelphia, 1874, i., p. 175.



by the fact that solutions containing this acid, such as bitter-almond and cherry-laurel water, very easily produce the same incidental effects.

Small doses (ten drops) of cherry-laurel water may excite tickling in the throat and increased flow of saliva. If this dose be somewhat increased, as is so commonly done in practice, or if small doses be frequently repeated, nausea, vomiting, dizziness, and headache appear not infrequently, as Coullon<sup>1</sup> has stated. With the sensation of giddiness may be associated buzzing in the ears, difficulty of respiration, and great weakness.

Upon the ground of these facts, and in view of the greatly varying strength of waters containing prussic acid, and also the great differences in the susceptibility of individuals to the action of this agent, Köhler<sup>2</sup> justly protests against its employment in large doses as an antispasmodic, a practice usually regarded as devoid of danger. It has been best described by Trousseau and Pidoux, who said of it that it is often dangerous, nearly always useless, and very rarely beneficial.

### SEMEN COLCHICI.

#### *Tinctura—Vinum Colchici.*

The activity of the preparations of colchicum depends upon the proportion of colchicia which they contain. This, however, varies with the season in which the plant is gathered. According to Aschoff and Bley,<sup>3</sup> colchicum root is richest in colchicia during the months of July and August. It is not impossible that this circumstance is influential in determining the abnormal phenomena which

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<sup>1</sup> Coullon: Recherches et considérat. médic. sur l'acide hydrocyan. Paris, 1819.

<sup>2</sup> Köhler: Handbuch der physiolog. Therapeutik. Göttingen, 1876, p. 1233.

<sup>3</sup> Aschoff und Bley, Archiv d. Pharmacie, Januar, 1857.

sometimes follow the therapeutical employment of the drug.

After small doses, 0.1–0.3 gram (gr. iss.–ivss.) of the seed, a burning sensation in the throat and stomach, ptialism, distressing nausea, and watery stools, with rectal tenesmus, are frequently observed. Some, or all these phenomena appear in some cases only after the long-continued use of the agent, but, in others, they may occur soon after taking it. With them are not infrequently associated, but with greater rarity, a feeling of fulness of the head, dizziness, and headache. The secretion of urine may also be attended with pain.

The symptoms which originate in the stomach, intestines, and kidneys should be regarded as the result of a local irritation set up by the drug. This statement is substantiated by the fact, which has been established toxicologically, that, in both man and animals, intense inflammatory changes in the mucous membranes of these organs may be found after large poisonous doses of this drug.

The above-described incidental effects of colchicum are most frequently observed after the use of the wine of colchicum seed, the dose of which is usually given as two grams (fl. 3 ss.), or six grams (fl. 3 iss.) daily. This is certainly too large, if the preparation is made from the fresh active plant.

The action on man of colchicia (which is officinal in the Pharmacopœia Austriaca) has been studied by Schroff.<sup>2</sup> After taking 0.01 gram (gr.  $\frac{1}{8}$ ), there appeared at first a bitter taste, later, a tickling sensation in the mouth, and soon afterwards eructation, nausea, inclination to vomit, and salivation. After 0.02 gram (gr.  $\frac{1}{4}$ ), besides these symptoms, vomiting and diarrhœa occurred, with tenesmus, and also a feeling of chilliness, and sleeplessness.

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<sup>1</sup> Monneret, *Archive génér. de Médecine*, 1844.

<sup>2</sup> Schroff, *Oesterreich. Zeitschr. f. pr. Heilkunde*, 1856 ii., 22.

## FOLIA DIGITALIS.

*Extractum—Tinctura—Infusum Digitalis.*

Digitalis, in common with only a small number of other drugs, possesses the peculiar faculty (which is probably due solely to an unusually slow elimination through the kidneys) of unfolding its action in the body during a relatively long period, and, therefore, of developing cumulative effects when repeated doses are administered. These may, under certain circumstances, produce threatening phenomena, or even symptoms of poisoning, among which are headache, dryness of the throat, nausea, and a sensation of choking, and, in well-marked cases, buzzing in the ears, disturbances of vision (manifested by the appearance of sparks before the eyes, amblyopia, or diplopia), also dizziness, swooning, vomiting, diarrhoea, sleeplessness, a thready, scarcely appreciable, and sometimes arrhythmical pulse, and a very great fall in the bodily temperature, a result of the slowing of the circulation. A headache, which appeared after even 0.03 to 0.09 gram (gr. ss.-iss.) was a prominent symptom in many cases. In a large number of patients, even 0.15 gram (gtt. iiij.) of the tincture sufficed to produce the above-mentioned phenomena.

In the absence of a true antidote for digitalis, the treatment of these symptoms consists in the administration of symptomatic remedies, stimulants, irritants to the skin, etc. From a prophylactic stand-point, special attention should be paid to the cumulative power of the drug, which may sometimes cause sudden death from paralysis of the heart, particularly when the agent is to be taken for some time, and its use must be stopped on the first appearance of abnormal subjective symptoms.

An observation of Traube<sup>1</sup> on an affection of the skin

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<sup>1</sup> Traube, Charité-Annalen, Jah. g. i., p. 622 u. Jahrg. ii., p. 19. Beiträge zur Pathologie u. Physiologie, Bd. ii., I. Abth., pp. 130, 136, 164.

after the use of digitalis, should be mentioned as a very rare occurrence. In a case of pleuritis and pericarditis, the patient took, from the fourth to the sixth day of his illness, 3.75 grams (gr. lvii.) of digitalis in an infusion. Four days after the last dose, there appeared, while the bodily temperature was normal, an erysipelatoid affection of the face, which resulted, five days later, in an excessive ragged desquamation. In a second case of pleuro-pneumonia, 4.08 gram (gr. lxi.) of digitalis were taken in five days in the form of an infusion. Four days after taking the last dose, the patient, who had hitherto been free from fever, experienced a rise in temperature, and, on the fifth day, there appeared on the body, the supinator surfaces of the forearms, and the backs of the hands, a papular exanthema, made up of quite prominent, carmine-red, rounded spots, disappearing on pressure, the majority of which united to form large patches elevated above the surface of the skin. On the next day, desquamation began on the face in tolerably large masses, while new eruptions showed themselves on the upper arms and neck. Four days later still, the exanthema had almost entirely disappeared, and not until some time afterwards, during the course of a newly-developed typhoid affection, did desquamation, in large flakes, occur on the body and extremities.

A similar exanthema, spreading over the whole body, was observed by Schuchardt,<sup>1</sup> in the case of a young robust man who had taken digitalis for a long time for the relief of endocarditis. When the same patient took digitalis again, one year later, the same eruption appeared with equal intensity.

It is perhaps not unimportant, in order to facilitate the comprehension of the manner of occurrence of this affection, to call attention to the fact that an ointment prepared from fresh digitalis leaves with lard may excite slight

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<sup>1</sup> Schuchardt: *Handbuch der Arzneimittellehre*. Braunschweig, 1858, p. 553.

inflammation and the eruption of a papular exanthema, when several times rubbed upon the healthy skin. More intense inflammation is produced upon the skin deprived of epidermis. In view of this fact, one can readily imagine that, when a certain individual disposition is present, the collection of a large quantity of the active principle of digitalis in the vascular channels may produce the same irritative effect upon the skin as the external application of the drug. This explanation is also supported by the fact that, in Traube's cases, the exanthema first appeared after the use of digitalis had been suspended.

Worthy of notice is a statement of Reil, that cumulative effects are very rarely observed after the administration of digitalin, on account of the appearance of certain forerunners of intolerance of this agent, which often render its abandonment absolutely necessary. These are a sensation of weakness in the epigastrium, inclination to vomit, exhaustion, dimness of vision, and heaviness of the head.

#### CHLORALUM HYDRATUM CRYSTALLISATUM.

The occurrence of incidental effects after the internal use of the hydrate of chloral is, in view of the very extensive employment of the agent, by no means common. Even its habitual employment, which is very common, particularly in England and America, leads, as Richardson<sup>2</sup> states, to no habituation of the drug, even in "chloral-drinkers," and produces no deleterious effects, as long as the permissible doses are not exceeded. Liebreich<sup>3</sup> has made the same statement upon the basis of reports from insane asylums, and has at the same time called attention

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<sup>1</sup> Reil: *Materia Medica der reinen Pflanzenstoffe*. Berlin, 1857, p. 155.

<sup>2</sup> Richardson, *Medical Times and Gazette*, February, 1871.

<sup>3</sup> Liebreich, *Deutsche medic. Wochenschr.*, 1877, No. 27, und Berlin, klin. Wochenschr., 1874, p. 50.



to the fact that, when a pure preparation is used to produce an hypnotic effect, even during long periods, no increase in the dose is necessary, and that unpleasant effects are not observed, in which respects this drug differs from opium and its alkaloids. He also says that an impure chloral presents a constantly increasing acid reaction and exerts perverse therapeutic effects, in consequence of the formation of noxious chlorine compounds.

The bad quality of the drug, which is usually the case with those preparations which are not well crystallized, is probably one of the causes of those cases of death after one or more medicinal doses, which are recorded in the literature of the subject. It is a significant fact, in this connection, that, during the early years of the employment of chloral, many such cases were reported, while, on the other hand, in recent times, when improved methods of preparation have been employed, such accidents are very rarely described. When they do occur, it is natural to regard the impurity of the preparation used as their cause, particularly in view of the fact that we are familiar with several organic chlorine compounds which are capable of exerting deleterious effects, even in small doses. At the same time, individual predisposition to the occurrence of such phenomena also plays a rôle, and the condition of the absorbing organs should by no means be left out of consideration.

It is characteristic of the cases of death after chloral, reported by various authors, that they occurred almost immediately or a short time after taking the drug, and usually during an attack of anxiety. Such cases have been reported, among others, by Nötel,<sup>1</sup> after four grams (3i.) of chloral; Jolly,<sup>2</sup> of two insane persons after five grams (gr. lxxv.) each; Marsh,<sup>3</sup> of four persons, the major-

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<sup>1</sup> Nötel, Virchow-Hirsch's Jahresbericht f. d. ges. Medicin, 1872, ii., p. 11.

<sup>2</sup> Jolly, Bair. ärztl. Intelligenzblatt, 1872, No. 13, 14.

<sup>3</sup> Marsh, Virchow-Hirsch's Jahresb., 1875, I., p. 479.

ity drunkards, after three grams (gr. xlv.), and Fürstner,<sup>1</sup> that of a girl, after two grams (3 ss.). The published results of autopsies give no information as to the causes of death.

According to Kern,<sup>2</sup> disturbances of the respiratory processes are excited in rare instances, which may increase from a feeling of anxiety, terror, and shortness of breath, to attacks of dyspnœa, and even asphyxia. Shaw<sup>3</sup> also, after about one gram (gr. xv.) of chloral, observed spasmodic breathing with irregular action of the heart. Marsh states that after an ordinary dose of chloral he has found changes in the mucous membrane of the respiratory apparatus, as shown by the occurrence of acute bronchitis.

Much more common than the above-mentioned phenomena is the occurrence of conjunctival irritation after one or repeated doses of chloral. Redness and swelling of the membrane are observed, disappearing on the discontinuance of the administration of the drug. Steinheim<sup>4</sup> treated a lady suffering from asthmatic attacks, who on three occasions experienced a severe disorder of vision every time she took chloral. It appeared in the form of dimness of sight, or complete blindness.

The condition described by Schüle<sup>5</sup> as chloral-rash, which is characterized by flashes of heat, and cerebral congestion with injection of the conjunctivæ, occurs only when alcoholic beverages have been taken after the administration of chloral.

Among other incidental effects, Curschmann<sup>6</sup> reported swelling of the epiglottis and false vocal cords, and Reimer<sup>7</sup>

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<sup>1</sup> Fürstner, Arch. f. Psychiatrie, Bd. vi., 1876, p. 344.

<sup>2</sup> Kern, Allgem. Zeitschrift f. Psychiatrie, 1872, p. 316.

<sup>3</sup> Shaw, Virchow-Hirsch's Jahresber., 1871, i., p. 334.

<sup>4</sup> Steinheim, Berlin, klin. Wochenschr., 1875, p. 77.

<sup>5</sup> Schüle, Zeitschrift f. Psychiatrie, Bd. 28, p. 4.

<sup>6</sup> Curschmann, Deutsches Archiv f. kl. Medicin, Bd. viii., p. 151.

<sup>7</sup> Reimer, Zeitschrift f. Psychiatrie, Bd. 28, p. 316.

the occurrence of decubitus. The ætiological connection of the latter with the use of chloral is, however, very doubtful. According to Reimer, bed-sores produced by the use of chloral are distinguished from the ordinary variety caused by long-continued pressure, by the fact that the former develop under very slight external pressure, while the epidermis is still intact, and spread deep down into the subcutaneous cellular tissue.

Here and there in the literature of chloral, cases are reported in which icterus is said to have occurred after the use of this agent. Thus Wernich<sup>1</sup> reports four observations, in which, after the use of chloral, a pre-existing jaundice became intensified, and also the case of a drunkard, in which a fresh icterus appeared after four grams of hydrate of chloral were taken. Arndt<sup>2</sup> also witnessed the occurrence of this condition in a paralytic, after he had taken the drug for fourteen days. The icterus passed off when the medicine was stopped, and reappeared when it was again used. Somewhat hazardous is an opinion of Gellhorn,<sup>3</sup> that, among others, atrophic affections of the liver of a very peculiar nature, may appear as the expression of an idiosyncratic action of chloral. This observation stands alone in literature.

Besides the phenomena already cited, eruptions upon the skin, either polymorphous or simple, have been observed in some persons either immediately or some time after the use of chloral in varying doses. They may be classified as the erythematous, the urticaria-like, and the eczematous forms.

I. *The erythematous form* is relatively the most common. In it the semblance of a diffuse hyperæmia is usually observed upon the face and neck. In other parts of the

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<sup>1</sup> Wernich, Deutsches Archiv f. klin. Medic., Bd. xii., p. 32.

<sup>2</sup> Arndt, Archiv f. Psychiatrie, Bd. iii., Heft 3.

Gellhorn, Zeitschrift f. Psychiatrie, Bd. 28, p. 625.

body, the erythema generally appears in the form of roseola-like or dark-red spots with irregular outlines, which bear a striking resemblance to purpura. According to Schülle (l. c.), it seems to follow by preference the course of the larger nerve-trunks. It disappears when the use of the drug is suspended. In one case, Brown<sup>1</sup> observed an inflammatory redness which spread uniformly over the whole body, while Husband,<sup>2</sup> in the case of a female patient, who for eight days took each day two doses of 1.3 gram (᠑i.) each, and for five days two doses daily of two grams each (3 ss.) each, witnessed the occurrence of a scarlatina-like exanthema, attended with high fever and increased sensitiveness of the skin, after the disappearance of which abundant desquamation occurred. Köbner<sup>3</sup> also reports a case in which, after the long-continued use of chloral, there appeared not a simple hyperæmic redness, but an erythema exsudativum which spread over nearly the whole of the body. It bore a very close resemblance to scarlatina, but the skin was much more swollen and infiltrated than in this disease. The eruption burned and itched, and, as the use of chloral was persisted in, ended in desquamation only after four or five weeks.

II. *The urticaria-like form* has been observed by Gauchet<sup>4</sup> and Chapman<sup>5</sup> among others. The latter saw it occur in the case of a lady who for fourteen days took one gram (gr. xv.) of chloral each evening. After this time an erythema showed itself, which passed off when the use of the drug was stopped, and when it was again administered two days later, the skin over the whole body quickly became covered with wheals, and the seat of a feeling of heat. Hypersecretion of the conjunctivæ appeared at

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<sup>1</sup> Brown, *Lancet*, 1871, Vol. i., p. 440.

<sup>2</sup> Husband, *eod. loco*, 1871, No. 25.

<sup>3</sup> Köbner, *Berl. klin. Wochenschrift*, 1877, p. 327.

<sup>4</sup> Gauchet, *Bulletin génér. de Thérapeut.*, 1871, p. 429.

<sup>5</sup> Chapman, *Lancet*, 1871.

the same time. With this urticaria-like form must also be classed those eruptions which have been described as a papular exanthema, which appear under the same circumstances. Thus Arndt (l. c.); after the use of chloral for eight days, found a papular exanthema which covered at first the extensor surfaces of the upper extremities, and later the entire body. It came and went, in accordance with the use or abandonment of the drug. Kern (l. c.) observed a similar eruption located upon the arms.

3. If the administration of the chloral be persisted in, the nodules may develop into vesicles with serous or purulent contents, and these, when they burst, may present a complete resemblance to *eczema*. This occurrence is, however, very rare, and seems to be represented in literature by only one case, which was studied by Kern. This is, however, not a typical case, because during the existence of the eruption, quinine was administered hypodermically, a drug which is itself capable of producing a variety of dermatoses. On the person of a robust woman, the subject of puerperal mania, there appeared on the ninth day of the administration of chloral, an exanthema attended by fever, and at the same time swelling of the face, the cheeks, eyelids, and ears. After a while the eruption grew paler, but reappeared when chloral was again taken, and the skin now presented, in a widely-varying manner, the appearance at one time of an impetiginous, at another of a moist, and at still another that of a squamous eczema or an ichthyosis, on account of the fact that the process of desquamation was not limited, as in the acute exanthemata, to a short period, but lasted for many weeks, during which time large masses of epidermis were cast off from all parts of the body. In a later period of the disease, the disturbances of the skin were marked by an extensive falling out of the hair of the head, and by a gradual casting-off of all the nails of the upper and lower extremities.

Schülle and others regarded a paralysis of the vasomotor



nerves, produced by chloral, as the direct cause of the affections of the skin.

As in the case of other drugs, attempts have of course been made to explain the occurrence of the above-described incidental effects of chloral. Some authors regard them as the result of a chronic blood-poisoning, which is developed only when the organism is saturated with the drug. If this be accepted, we must attribute a cumulative action to chloral, such as digitalis has already been shown to exercise. This hypothesis is, however, on a closer examination of the conditions really present, shown to be untenable. By a blood-poisoning we understand such a chemical or physical alteration of the elements of the blood that they are no longer capable of performing their normal functions. In this sense one may speak of blood-poisoning by inhalation of carbonic oxide or sulphuretted hydrogen, by taking too large doses of chlorate of potassium, or by the entrance of any other heterogeneous substances into the vascular channels. But in all these instances there occur changes in the blood which can be objectively demonstrated, either by the spectroscope or the microscope, or even by inspection. No such mode of action has, however, been yet demonstrated for chloral, and we are, therefore, not justified in admitting the occurrence of blood-poisoning in this instance. Neither can it be a certain definite degree of saturation of the organism with chloral which produces the incidental effects, for they show themselves, in some instances, even after one small dose. If, on the other hand, such a degree of saturation were really produced, a cumulative action of chloral would also occur, and this would suffice to maintain sedative or hypnotic effects for a long time, without further administration of the drug. That such is not the case requires no proof. Other factors must, therefore, co-operate in the production of the symptoms described. They are most naturally explained by the general facts already discussed

in the introduction to this work. It is probable that the chloral (or its products of decomposition) which reaches the different organs, exerts an irritant or a depressing action upon some persons, either in consequence of an abnormal distribution of vessels, or of other individual peculiarities. These effects last as long as the products in question remain in the body. Their occurrence may also be facilitated by bodily conditions which cause a retardation or an arrest of the elimination of waste material.

No especial treatment is necessary for the relief of the above-described effects of chloral, since they disappear spontaneously on the discontinuance of the drug. The fever which usually attends chloral eruptions also requires no treatment, because quinine, as Schülle states, has no effect, and cold baths are of slight utility. It must also be remembered, that, particularly in persons who possess a certain disposition to the occurrence of drug-eruptions, the administration of quinine may easily induce a variety of complications, so that it is on the whole better to abstain from its use.

#### CHLOROFORMUM.

Soon after the introduction of chloroform into medical practice, and in the midst of its progress through the civilized world, cases were made public in which persons, while under its influence, did not awake from their anæsthetic sleep. Although in the beginning of the employment of this agent, the reluctance to publish cases which ended in death could be explained by the circumstance that physicians, under whose care they occurred, attributed them to their own want of skill, the increasing number of such accidents soon made it seem probable that there must be certain definite factors which should be regarded as the causes of the so-called "chloroform deaths." Up to the present time, however, these have not been definitely determined, in spite of a very large number of

most careful clinical and experimental investigations. The symptomatic phenomena, on the other hand, which attend or precede death from chloroform, have been carefully studied and accurately described.

No warning prodromal symptoms precede the appearance of death in the minority of cases of fatal chloroform narcosis. The pulse stops suddenly, in either complete or incomplete anæsthesia, respiration ceases one or two minutes later, the face becomes pale, the pupils dilate, and the patient dies; but, as a rule, the fatal termination of an anæsthesia is indicated by one or two, or a series of premonitory symptoms. There occur obstinate vomiting, a striking pallor of the face, labored, sometimes stertorous breathing, excessive dilatation of the pupils, absence of reflex movement on touching the conjunctiva, spasmodic muscular movements, a certain rigidity of the muscles, and a small, almost imperceptible or irregular pulse, which entirely ceases in some cases, in spite of the continuance of the action of the heart. Respiration stops either before or simultaneously with the arrest of the pulse, or continues for a short while afterwards. In the former case, we recognize a death from chloroform by asphyxia, in the latter by syncope. Billroth<sup>1</sup> observed, just before a death from chloroform attended with convulsions, that a previously bleeding wound of a finger ceased to bleed.

Kappeler<sup>2</sup> has collected with great care the statistical data bearing upon death from chloroform, as far as they have been published. He reports one hundred cases, of which seventy-eight were of the male and twenty-two of the female sex. The highest mortality occurred between the ages of forty-six and sixty years, or 24.7 per cent. Next came the ages from thirty-one to forty-five years, with

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<sup>1</sup> Billroth, Wiener medic. Wochenschrift, 1868, No. 46.

<sup>2</sup> Kappeler, Anästhetika, Deutsche Chirurgie von Billroth und Lücke, Lief. 20, p. 100 u. ff.

20.7 per cent, while under five, only two, and over sixty, only one death occurred. The patients died before complete anæsthesia in forty-three cases, and during it in forty-seven. In eleven cases, no statement was made as to this point. In fifty-six fatal cases of anæsthesia, the inhalation was practised by means of cloth or lint, in five cases with Esmarch's chloroform-basket, and, in the same number, with Clover's inhaling apparatus. The quantity of chloroform used varied in forty-six cases between twenty drops and thirty to sixty grams (fl. ʒ i.-ij.), the average quantity being 11.1 grams (fl. ʒ ij. ʒ ij.). Of twenty cases, in which statements on this point are made, death occurred in ten in from six to fifteen, and in five, in from one to three minutes.

The pathological alterations which have been hitherto discovered, furnish, on account of their inconstancy and their general nature, no clear insight into the immediate causes of death. The investigation of the English Chloroform Committee, which were made, as a rule, upon dogs, showed, like many analogous observations on man, a great distention of all the cardiac cavities with blood, in which respect those of the right side surpassed those of the left. In some cases, bubbles of gas were found in the veins of men who fell victims to chloroform, as v. Langenbeck, among others, had already stated in the year 1848. This fact induced some French investigators to regard death from chloroform as due to a development of chloroform vapor in the veins, or as a consequence of embolism of the pulmonary capillaries produced by this gas. The renewed observation of the collection of gas in the vessels has recently led to an experimental investigation of this phenomenon. v. Recklinghausen, in three cases in which respiration had continued for some time after the cessation of the pulse, and death had then occurred, found bubbles of gas in the larger venous trunks and the heart, although no traces of decomposition could be discovered on the bodies. Son-

nenberg,<sup>1</sup> in his experiments upon animals, made in consequence of this observation, demonstrated the development in the vessels, of a gas which was found to be nitrogen, after the administration of chloroform, but failed to discover the exact conditions under which the process occurs. In his opinion, one may imagine either a mechanical separation of nitrogen, or its liberation, under peculiar conditions of pressure, inside the blood-vessels, in the presence of chloroform.

This demonstration of the liberation of a gas which takes place in the vessels after the inhalation of chloroform is of great importance, from a general toxicological stand-point, but leads us no nearer to an explanation of the fact that in rare cases, in spite of the greatest care in the administration of chloroform and in watching the patient, death occurs; while, on the other hand, when the same chloroform is used and much less care is taken, many other patients are anæsthetized without any unpleasant accident. Of course, a large number of conditions have, in the course of time, been advanced as the causes of badly-borne or fatal chloroform inhalations; but we have thus far not been in a position to regard any one of them as the universal and exclusive etiological factor in such cases. Therefore so apodictical a statement as that made by Sédillot,<sup>2</sup> and, later also, by Yvonneau<sup>3</sup>: "*Le chloroforme pur et bien employé ne tue jamais,*" cannot be accepted as proven, since there are probably other factors which may, under certain circumstances, cause the fatal termination of an anæsthesia.

All the conditions which have hitherto been held responsible for death from chloroform may be arranged in three groups. They comprise:

1. The quality of the chloroform.

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<sup>1</sup> Sonnenberg, *Tageblatt der Naturforscher-Versammlung zu Baden-Baden*, 1879, p. 29.

<sup>2</sup> Sédillot, *Gazette de Strassbourg*, 1851, 7, II.

<sup>3</sup> Yvonneau: *De l'emploi du Chloroforme*, Paris, 1853.



2. The method of administration.

3. The mental and bodily condition of the patient.

1. *The bad quality of the chloroform* is usually regarded as the most important of the causes which lead to the occurrence of hurtful incidental effects, or death, from its use. It is well-known that chloroform may be adulterated in various ways, either designedly or accidentally. The former consist in the addition of alcohol or ether, and the latter are either the result of the method of manufacture of the drug, or are due to its spontaneous decomposition under the influence of diffuse sun-light. The impurities which occur during the process of manufacture consist, as a rule, of either a mixture of acetyl and its chlorine derivatives, or of fusel oil, and are recognized by the production of a black or red color on the addition of concentrated sulphuric acid to chloroform. The products of the spontaneous decomposition of chloroform may be: free chlorine (shown by the appearance of a red color when chloroform is dropped into a dilute solution of iodide of potassium); hydrochloric acid (the chloroform becoming cloudy on the addition of nitrate of silver), and hypochlorous acid (the test for which is the bleaching of a strip of blue litmus-paper when dipped into chloroform). Higher-chlorine compounds may also be found in chloroform, such as ethene chloride (Dutch liquid), ethyl chloride, tetrachlorethene, ethidene chloride, trichlorethane, tetrachlorethane, allyl chloride, amyl chloride, and amylene and aldehyde.

All of these impurities of an organic nature, the majority of which may be qualitatively demonstrated, usually betray their presence by an alteration in the specific gravity and the boiling point of the chloroform. Official chloroform has a specific gravity of 1.596, absolutely pure chloroform at 15° C. (59° F.), a specific gravity of 1.502; at 17.5° C. (64° F.), of 1.497, and at 20° C. (68° F.), of 1.493.

The presence of one-half per cent of alcohol lowers its specific gravity to 1.493 at 15° C. (59° F.), of one per cent, to 1.485. Ether, ethene chloride, and amylene also lower the specific gravity, while tetrachlorethene, tetrachlorethane and trichlorethane raise it. The boiling point of officinal chloroform is always 61–62° C. (142° F.). It is lowered by ethylic chloride, ether, and amylene, and is raised by alcohol, ethylenic chloride, and the rest of the above-mentioned higher chlorine compounds. The English chloroform and that prepared from chloral, both of which are said not to undergo spontaneous decomposition, have a specific gravity of less than 1.49.

Nearly all the more highly chlorinated compounds which have been mentioned produce unpleasant incidental effects when inhaled, and are readily capable of causing bad accidents, particularly when certain predisposing bodily conditions are present. Although such adulterations have as yet been found in only a few of the recorded cases, it is evident that no careful investigation has been made in the majority of instances. Worthy of notice is an observation of Bartscher,<sup>1</sup> bearing upon the differences as regards their action upon man, between pure chloroform and that containing other chlorinated compounds. While he could very easily produce anæsthesia by using fresh chloroform, a preparation which had stood for several weeks caused a number of injurious effects, both during anæsthesia, as well as in the course of the succeeding twenty-four hours. That changes took place in the chloroform while standing, was shown by the fact that it at first lost its somewhat pleasant, sweetish taste, gradually acquired a burnt odor, and later produced disagreeable irritation in the nose and throat. In such cases, the presence of hydrochloric acid, alcohol, and ethene chloride in the chloroform, could always be demonstrated.

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<sup>1</sup> Bartscher, Berl. klin. Wochenschrift, 1866, p. 325.

The injurious incidental effects ceased when he began to administer rectified chloroform. Berghmann<sup>1</sup> found a small quantity of allyl chloride in a specimen of chloroform which had caused death during complete anæsthesia. In another case reported by Hüter<sup>2</sup> (death during complete anæsthesia), only one-third of the chloroform distilled over at the proper temperature ( $62^{\circ}$  C.,  $143\frac{2}{3}^{\circ}$  F.). The remainder boiled only at  $70-75^{\circ}$  C. ( $158-167^{\circ}$  F.); and even at  $80^{\circ}$  C. ( $176^{\circ}$  F.), a large residue remained. It contained neither hydrochloric acid nor free chlorine. It seemed to have been prepared from impure alcohol, and contained chlorinated products. In occurrences of this kind, one is compelled to regard the bad quality of the chloroform as an important factor in producing death, particularly when the patient was robust, and suffered from no pre-existing disease. In order to be secure against accidents of this kind, it is well to employ, according to the custom of Hüter, only a chloroform the boiling point of which has been previously determined.

2. *An improper manner of administration, i. e.,* the inhalation of chloroform insufficiently mixed with atmospheric air, is much more apt than pure chloroform to produce threatening phenomena or death. In England, particularly, the utmost weight is attached to this factor in the etiology of death from chloroform. Thus the English chloroform committee<sup>3</sup> expressed the opinion that those cases of death which occur before the beginning of anæsthesia, as well as those in which a fatal result takes place from syncope previous to the beginning of the stage of excitement, are due to the sudden inhalation of too concentrated vapors of chloroform. Holmgreen<sup>4</sup> has since

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<sup>1</sup> Berghmann, Refer. in Kappeler, l. c., p. 88.

<sup>2</sup> Hüter, Berl. klin. Wochenschr., 1866, No. 30.

<sup>3</sup> Medico-Chirurg. Transact., xlvii., 1864, p. 323.

<sup>4</sup> Holmgreen, Virchow-Hirsch's Jahresbericht, 1867, i., p. 450.

succeeded in proving, by experiment, that the slowing or arrest of the heart's action which appears after the inhalation of too concentrated vapors of chloroform, in the beginning of its administration, occurs in consequence of an influence reflected from the branches of the trigeminal in the nasal and pharyngeal mucous membranes upon the pneumogastric nerve. If these parts are protected from contact with the chloroform vapors, by causing them to be inhaled through a tracheal canula, these disturbances in the respiration and pulse fail to occur, as the chloroform committee found. Lallemand, Perrin, and Duroy<sup>1</sup> also witnessed the speedy occurrence of death in animals which inhaled the too concentrated vapors of chloroform. A mixture of four parts of chloroform with one hundred parts of air they found harmless, a mixture of eight parts to one hundred deadly. In order to avoid the dangers of too concentrated chloroform vapors, the chloroform committee established as the normal standard for inhalation a mixture of three and one-half parts of chloroform with one hundred parts of air, and, as a maximum, four and a half parts of chloroform to one hundred of air.

Apparatus for the preparation of this or similar mixtures have been constructed by Clover and others. They are, however, too complicated, and do not furnish a more certain protection against the dangers of chloroform, which lie in the degree of concentration, than the ordinary chloroform-basket in the hands of a man familiar with its use. By a gradual administration, beginning with small quantities of chloroform, and a free admission of fresh air to the respiratory passages, the accidents which may result from too high a degree of concentration of the vapor may be avoided with absolute certainty.

### 3. *The mental and physical condition of the patient far*

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<sup>1</sup> Lallemand, Perrin, Duroy: *Du rôle de l'alcool et des anesthésiques dans l'organisme*, Paris, 1860.

exceeds, in importance, both the factors already mentioned, in the production of dangerous conditions during the administration of chloroform; but just as little as we are justified in regarding the bad quality of the chloroform or its faulty administration as the sole cause of all deaths from this agent, or even of its hurtful incidental effects, just so little is the view permissible that any one of the conditions still to be mentioned is the exclusive factor in the production of perverse effects of the drug. The following conditions pertaining to the mental and bodily spheres, have by different authors been held responsible for such occurrences:

*a. An idiosyncrasy against chloroform.*

Clemens,<sup>1</sup> Billroth,<sup>2</sup> and Dénonvilliers<sup>3</sup> may be regarded as representatives of this view. The latter regards the death of those persons who die very suddenly after inhaling a few whiffs of chloroform, as due to an idiosyncrasy, and cites as analogues the specific action of other medicinal agents, such as iodide of potassium, etc., upon certain persons. Clemens states that he has often met with the chloroform idiosyncrasy, and that it is characterized by this peculiarity, that persons who submit to an operation with the earnest desire to pass through it without pain, with the aid of chloroform, spring up after the first few inhalations of the drug, and prefer to submit to the operation without anæsthesia. Dénonvilliers is of the opinion that the peculiar susceptibility to the toxic action of chloroform found in certain individuals is of only temporary duration, in view of the fact that patients who, a short time previously, have borne the first employment of the agent without unpleasant effects, may succumb to its

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<sup>1</sup> Clemens, Archiv f. Heilkunde, 1824, p. 500.

<sup>2</sup> Billroth, Wiener medic. Wochenschrift, 1868, No. 47.

<sup>3</sup> Dénonvilliers, Bulletin de l'Académie de Médec., Juin, Juillet, 1857, T. xxii.



second administration. In the introduction to this work, the attempt has already been made to furnish a substratum for the intrinsically meaningless conception of an "idiosyncrasy." If we understand by this term a certain bodily condition which, being congenital, consists either in an abnormal condition of the structure and the arrangement of any of the systems of the body, or is temporarily developed as a consequence of certain functional disturbances in individual organs, we can, in given cases, easily explain the deviations from the normal action of chloroform, *e. g.*, the ready occurrence of reflex arrest of the heart's action, or the appearance of exanthemata or vomiting.

*b. Psychological depression.*

According to the opinion of the English chloroform committee, persons who are under the influence of any emotion, such as fright, terror, care, etc., show a special disposition to succumb to the action of chloroform. The same is true of individuals who have received injuries from any suddenly exerted force, and present that group of symptoms known as "shock," consisting in mental apathy or unconsciousness, smallness of the pulse, pallor of the face, etc.

*c. Bodily weakness.*

It is a matter of indifference whether this condition was caused by prolonged sickness, excessive loss of blood, or venereal excesses. Paget<sup>1</sup> attributed the death of a girl who had led a very disorderly life, who was about to be brought under the influence of chloroform, in order to have a carcinoma of the vagina removed, and died after the first few inhalations, to her debilitated bodily condition, produced by her dissolute life. In order to elucidate this point, Clemens<sup>2</sup> made experiments upon dogs, rabbits, guinea-pigs, and large insects, which are said to have re-

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<sup>1</sup> Paget, *Lancet*, October, 1853.

<sup>2</sup> Clemens, *l. c.*, p. 504.

sulted in showing that after immoderate sexual indulgence, death from chloroform was much more quickly produced, and by much smaller doses, than in the case of healthy animals.

*d. Diseases of the heart, particularly fatty degeneration of the muscular tissue.*

Fatty degeneration of the heart, in spite of the negative results in this regard obtained by Kidd,<sup>1</sup> in persons who died during anæsthesia by chloroform, must be regarded as one of the most important adjuvants in the causation of death from this agent. In fifty-six such cases, Sansom<sup>2</sup> found it eighteen times, and in the list collected by Kappeler<sup>3</sup> it occurred sixteen times in sixty autopsies. In spite of this high percentage, Kappeler attributes only a relative, and not an absolute danger to fatty heart, because, on the one hand, among those who suffered from this affection, some had previously taken chloroform without accidents, and on the other, in amputations for senile gangrene, in which disease, as is well known, atrophy and fatty degeneration of the heart are common, he never saw any disquieting phenomena produced by the administration of the drug. This limitation of fatty degeneration of the heart to the position of an only relatively dangerous complication is entirely justifiable, because in view of the great frequency of its occurrence in a slight degree, investigation into the causes of death from chloroform in a given case may easily fall into wrong channels and lead to erroneous conclusions.

*e. Chronic alcoholism.*

It has not yet been explained why drunkards react in such an abnormal manner to the inhalation of chloroform, as is so often observed in operating-rooms. Such individuals require not only much larger quantities of chloro-

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<sup>1</sup> Kidd, British Medical Journal, 1862, January 25th, May 24th.

<sup>2</sup> Sansom: Chloroform, its action and administration. London, 1866.

<sup>3</sup> Kappeler, l. c., p. 121.

form than healthy persons, in order to be fully anæsthetized, but they also manifest intense excitement, as shown by excessive muscular activity, screaming and struggling, and in the unconscious endeavor to leave the operating table. In the condition of relaxation which follows this stage of excitement, there often occurs a state of collapse, attended with stertorous respiration, which may easily lead to a fatal result. It is natural to regard a combined action of alcohol and chloroform as the cause of these phenomena, attempts to explain which have been made from different stand-points. Lefort is of the opinion that the organism weakened by alcohol is unable to bear the action of chloroform—an explanation which amounts to nothing more than a statement of the fact. According to Scheinesson,<sup>1</sup> chloroform causes both a lessening of heat production and a retardation of the bio-chemical processes which take place in the organism. Alcohol produces the same effect, and the sum of their united actions may, in the case of drunkards, induce deleterious incidental effects or even fatal results. It is difficult to believe that such processes—lowering of temperature and diminution of the chemical processes of the body—can take place in so short a time as from the beginning of anæsthesia to the production of sleep, and exert so powerful an action. The opinion seems much more plausible, that the material changes produced in the central nervous system by chronic alcoholism manifest themselves, during the action of chloroform, by functional changes of a higher degree, and in a much more deleterious manner, than in the case of an ordinary debauch in alcoholic beverages. From this point of view all the abnormal symptoms would be regarded as either directly or indirectly of central origin.

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<sup>1</sup> Scheinesson, Untersuchungen über den Einfluss des Chloroforms auf die Wärmeverhältnisse der Organe und den Blutkreislauf. Dorpat, 1863, und Archiv der Heilkunde, Bd. x., 1861.

According to the data collected by different authors, the proportion of deaths from chloroform occurring in drunkards varies between ten and thirteen per cent.

In the preceding pages we have discussed the causes which, singly or combined, may lead to death from chloroform, and have also indicated the symptoms which attend it. It is fortunately comparatively rare, occurring about once in three thousand cases of the administration of the agent, and it is probable that this proportion would be rendered still smaller by a more careful investigation of the real causes of such accidents. The attainment of this result, a diminution of the death rate, would be also much facilitated by a careful attention to the trivial abnormal phenomena which occur in the majority of cases, and not infrequently, as has been already remarked in the beginning of this article, precede death from chloroform.

Among these is the tonic spasm of the muscles of mastication, and the posterior muscles of the tongue, which frequently occurs during the stage of excitement. The tongue is spasmodically drawn backwards by the styloglossal and stylo-pharyngeal muscles, and therefore presses the epiglottis downwards. In this manner a mechanical closure of the entrance to the larynx is produced, and if this be not at once relieved, mechanical suffocation occurs, attended with lividity of the lips, exophthalmus, etc.

Another disagreeable incidental effect is vomiting, which appears in all stages of anæsthesia. It nearly always appears when the stomach is full, and may become so obstinate as to last even twenty-four hours after completion of the anæsthesia. It is usually attended with thirst, headache, and depression of spirits. An entrance of the contents of the stomach into the air-passages occurs but rarely while it is present, as the patients usually wake up when it begins. In the one hundred cases of death collected by Kappeler, death from suffocation in this manner occurred only twice.

In rare instances, icterus and the passage of the coloring matter of the bile into the urine have been observed after the inhalation of chloroform.

The greatest attention is, however, demanded by the phenomena pertaining to the organs of respiration and circulation. It has already been stated that reflex apnœa may occur after the first few inhalations of chloroform. In this event there suddenly occurs, once or repeatedly, a pause in respiration, lasting a shorter or longer time, or the respiratory acts become constantly slower and more shallow, or inspiration fails entirely, after a long jerking expiration. These phenomena either disappear spontaneously or are easily relieved by the aid of the physician. Irregularity or complete failure of the pulse, attended with pallor of the face, is also a common occurrence. These symptoms may also disappear spontaneously, in strong contrast with that group of phenomena known as chloroform-syncope, in which the radial pulse suddenly disappears, the heart-sounds become almost inaudible, the respiration ceases, and the face becomes like that of a dying man. Restoration to a normal condition is possible in very few such cases.

Another incidental effect of chloroform, interesting only from a pathognostic standpoint, was observed by Richet.<sup>1</sup> During a normal anæsthesia, there appeared dark-red spots, spread over the whole body, which presented the appearance of a purpura hæmorrhagica, but disappeared under pressure.

Of almost equal interest with these incidental effects produced by the inhalation of chloroform, are those excited by the application of this agent to the healthy skin or mucous membranes. Redness and a feeling of pain are produced by rubbing chloroform upon the normal skin, and not infrequently there appears an urticaria-like or an

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<sup>1</sup> Richet, *Journal de la Société des Sciences méd. de Bruxelles*, 1851.



eczematous eruption. Vesiculation may occur if the application be continued. When chloroform is applied to certain very sensitive portions of the skin, *e. g.*, the scrotum, the pain which it causes is so intense and persistent that patients generally refuse to allow a renewed employment of the agent. For this reason it is not advisable to follow the method of treating orchitis recommended by Bouisson,<sup>1</sup> enveloping the scrotum in compresses saturated with chloroform.

Upon wounds and mucous membranes, chloroform produces pain of a relatively much more intense degree. When it falls upon the lips during anæsthesia, fissures sometimes form upon the affected parts, or the mucous membrane is thrown off in flakes.

*Treatment of Accidents from the Use of Chloroform.*

The disturbances in the respiration and pulse demand energetic interference more than all others. Mechanical closure of the rima glottidis by the spontaneous falling back of the tongue, or in consequence of the spasmodic traction exerted by the posterior lingual muscles, is relieved by forcing open the mouth, by Heister's speculum, if necessary, and by drawing the tongue forcibly forwards by the tongue-forceps or a loop of thread, and cleansing the mouth from mucus. In many cases, the same end is accomplished by the more simple manipulation of lifting the lower jaw, as described by Heiberg.<sup>2</sup> The operator stands behind the reclining patient, places the thumbs on the symphysis of the lower jaw, presses the second joints of the flexed index fingers behind the posterior borders of the ascending ramus of the jaw, thus holding the entire bone firmly between his hands, and draws it forcibly forwards. In order to accomplish the same

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<sup>1</sup> Bouisson, *Annales des maladies de la peau*, Janvier, 1851.

<sup>2</sup> Heiberg, *Berliner klin. Wochenschr.*, 1874, p. 449.

object, Kappeler stands before the patient, places his thumbs close to the nose of the patient, upon the anterior wall of the upper jaw, and with the two distal phalanges of his bent index fingers, placed behind the angles of the lower jaw, draws the bone forwards. In this manœuvre, the tongue and the hyoid bone are also drawn forwards, and the epiglottis, which follows them, is placed upright.

If, in spite of the fact that air has free access to the lungs, there occur disturbances of respiration and circulation, simultaneously with a change in the color of the patient's face, the use of chloroform should be immediately stopped, an abundance of fresh air provided for, and, if the anæsthesia be still incomplete, as shown by the fact that the organism still responds by reflex movements to external irritation, recourse should be had to cold douches and injections of cold water into the nasal cavities, and the patient should be made to inhale strongly-smelling substances, such as ammonia or its carbonate. Billroth<sup>1</sup> is, however, perfectly right in insisting that no time should be wasted with such measures in complete anæsthesia, in which they can be of no possible use, but the operator should at once resort to artificial respiration.

A number of methods have been recommended for this purpose, such as :

1. Inflation of the lungs from mouth to mouth, while expiration is aided by compressing the lower part of the thorax, and the nostrils are kept completely closed. In using this method, as Billroth observed, a portion of the air goes into the stomach.

2. Inflation by means of bellows. Plouviez<sup>2</sup> introduced the nozzle of a bellows into one nasal opening or into the throat, and suddenly forced a stream of air into the lungs.

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<sup>1</sup> Billroth, Wiener medic. Wochenschrift, 1868, p. 795.

<sup>2</sup> Plouviez, Journal de la Soc. des Sciences médic. de Bruxelles, 1857, p. 14.

The breast and abdomen of the patient were at the same time alternately compressed.

3. Inflation by means of a laryngeal catheter. If it be impossible to introduce a catheter into the larynx, on account of spasm of the posterior lingual and upper pharyngeal muscles, tracheotomy must be performed, and air introduced through the tracheal canula by the mouth or bellows.

4. The method of Marshall Hall, in which the patient, several times in each minute, is laid first upon the back and then upon the side, at regular intervals, pressure being exerted upon the back every time the body is turned over.

5. Galvanization of the phrenic nerve. The positive moistened electrode of a constant battery or a sliding induction apparatus is placed upon the phrenic nerve in the neck, over the *scaleni* muscles, and the negative over the precordium, under the edge of the ribs, or both poles are placed on the sides of the neck, at the outer edges of the *sterno-cleido-mastoid* muscles.

6. Allowing the patient's head to hang down, as recommended by Nélaton, or suspending the body by the feet, the proceeding adopted by Spoerer<sup>1</sup> in one case with success.

7. Acupuncture or electropuncture of the heart. This was attempted by Hüter<sup>2</sup> in a case of arrest of the heart's action, as a last resort, but without success. He introduced a needle two inches long at the left edge of the sternum, into the fourth intercostal space, to a depth of three-quarters of an inch, and a second at a point nearer the nipple, and somewhat lower down.

The occurrence of one or more attacks of vomiting during anæsthesia, or on awaking from it, rarely requires the-

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<sup>1</sup> Spoerer, *Petersburger medic. Zeitschrift*, 1866, p. 110.

<sup>2</sup> Hüter, *Berliner klin. Wochenschr.*, 1865, p. 486.

rapeutic interference. If it become more frequent, pieces of ice, or champagne should be administered. The application of cold compresses to the epigastrium usually succeeds in arresting it.

#### IODOFORMUM.

After the administration of iodoform, aside from the odor which attends its elimination, only such incidental effects have been hitherto observed as are due to a central action of the agent. After Italian authors had called attention to the anæsthetic or hypnotic effects of this drug, Binz<sup>1</sup> showed that this action was due to a liberation of iodine in the body. "Since a yeast-cell, when touched by iodine, decomposes no more sugar, and a colorless blood-cell sends out no more processes, a brain-cell, under the same influence, suspends its peculiar activity; it no longer receives impressions from without, and ceases to produce impulses for its centrifugal filaments. It sleeps, if the condition produced by iodine be reparable; it dies, if its structure has been organically altered."

Proof of the correctness of this deduction is furnished by a few cases communicated by Oberlaender,<sup>2</sup> among others, in which incidental effects of central origin were produced by the use of iodoform. A female patient, affected with gummy tumors, took forty-two grams (3 xss.) of iodoform in the form of pills, during a period of eighty days. At the expiration of this time, she was attacked by dizziness, a feeling of weakness, and diplopia. These symptoms lasted two days and a half. In spite of the discontinuance of the remedy, she began to vomit and fell into a deep sleep, from which she could be aroused

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<sup>1</sup> Binz, *Archiv f. experiment. Pathologie u. Pharmakologie*, Bd. viii., p. 310 u. Bd. xiii., p. 159.

<sup>2</sup> *Deutsche Zeitschrift für pr. Medicin*, 1878, No. 37. Ref. in *Archiv für Dermatologie und Syphilis*, 1879, p. 372.

with great difficulty. For several days this drowsiness alternated with conditions of excitement, foolish talking, a feeling of great anxiety, and twitchings of the muscles of the face and trunk. Not before the twelfth day after the beginning of these symptoms was she able to stand alone and walk a short distance.

The second case was that of a person affected with ulcers of the throat, who had taken five grams (gr. lxxv.) of iodoform in pills, in seven days. Somnolence appeared, the gait became clumsy and uncertain, and the patient complained of headache over the whole circumference of the head. After these symptoms had lasted for one day, she fell into a comatose condition, which lasted five days, during which time, however, she reacted promptly to external irritation, making warding-off gestures. Articles of food were swallowed. The urine gave a distinct iodine reaction. Not until fourteen days after the appearance of the first symptoms of disease could the patient be regarded as cured.

The probability of confounding such conditions with cerebral syphilis is not great, because in the latter no improvement is obtained by expectant treatment.

#### METHYLENI BICHLORIDUM.

The bichloride of methylene, or chloromethyl, has been much employed since the year 1867, when Richardson first recommended it as an anæsthetic. It was said to be preferable to chloroform on account of being less dangerous, and producing only insignificant incidental effects, or none at all. But it has been since discovered that this substance has no particular advantages over chloroform, and is hardly less dangerous. Holländer,<sup>1</sup> who used it during the extraction of a tooth, was compelled in one case to administer nearly thirty grams (℥i.) in

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<sup>1</sup> Holländer, Berliner klin. Wochenschrift, 1867, p. 49.



order to produce anæsthesia, and afterwards noticed a condition of excitement, violent vomiting, and a feeling of fulness of the head, which lasted nearly an hour after the patient had regained consciousness. Hegar and Kaltenbach<sup>1</sup> witnessed the occurrence of attacks of asphyxia after the inhalation of the bichloride of methylene, and found excoriations on the lips and cheeks, when it was administered by the ordinary wire basket, instead of Junker's apparatus.

In addition to these trivial accidents, fatal results have also been known to occur after the use of this agent. They took place either suddenly without respiratory disturbances or change in the color of the face, or the respiration became gasping, the radial pulse small and fluttering, the color of the face pale or livid, and death followed, with absolute cessation of the pulse, but without convulsions.

#### ÆTHYLIDENI CHLORIDUM.

Ethylidene chloride, which has been recommended as an anæsthetic,<sup>2</sup> and occasionally successfully employed for this purpose, a fluid which boils at 60° C. (140° F.), produces a speedy and quiet anæsthesia, with equable action of pulse and respiration. Nevertheless, the further employment of the agent has been arrested by the occurrence of a death during anæsthesia produced by it.

#### ÆTHER SULPHURICUS.

Like chloroform, ether produces during its inhalation a number of accidents which are either of a transitory nature or lead to fatal results. Among the former is an obstinate vomiting which may continue not only during anæsthesia, but also after the operation, and paroxysms of coughing.

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<sup>1</sup> Hegar u. Kaltenbach: *Operative Gynäkologie*, 1874, p. 25.

<sup>2</sup> O. Liebreich, *Berliner klin. Wochenschr.*, 1870, No. 31.

The latter is probably due to the fact that, in consequence of the free secretion from the salivary glands which always takes place during etherization, saliva flows into the air-passages.

The dangerous symptoms are those which pertain to the respiration and circulation. Paleness or cyanosis of the face appear, the respiration at the same time becomes irregular or ceases entirely, and the pulse becomes small and finally imperceptible. Cases have been published in which, although the patients had reached this dangerous state, restoration was successfully accomplished by the aid of artificial respiration, drawing the tongue forwards, etc. If, however, the whole mechanical therapeutical apparatus is not at once employed against these disturbances, death occurs suddenly, either with simultaneous cessation of the respiration and pulse, or persistence of the latter for a few minutes longer than the former. In the majority of the cases reported by English authors, death occurred without premonitory symptoms. In some there appeared violent muscular excitement, cyanosis or turgescence of the face, dilatation of the pupils, or labored breathing.

The measures to be employed for the relief of such phenomena are the same as those recommended in syncope from chloroform. In order to prevent them, the head of the patient must be elevated so as to obviate the entrance of saliva into the air-passages. Attention must also be paid to the degree of concentration of the ether-vapors, and the purity of the preparation used, as in the case of chloroform.

The habitual use of ether, as Ewald<sup>1</sup> observed in the case of a so-called "ether-breather," causes general weakness, muscular tremors, and a peculiar annoying odor of the body.

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<sup>1</sup> Ewald, Berliner klin. Wochenschrift, 1875, p. 133.

## AMYLI NITRITUM.

The nitrite of amyl, a product of the action of nitric acid upon amylic alcohol, was regarded, during the early years of its employment, provided that it contained no noxious ingredients, such as hydrocyanic and nitric acids, as a harmless substance which produced no disquieting phenomena. Incidental effects upon the functions of various organs have, however, since been frequently observed after the use of this agent. Their appearance is dependent upon the individuality of the patient, but they occasionally occur also in persons who are accustomed to the inhalation of the drug.

Among the organs of special sense, the eye is most frequently affected in this respect. The subjective color-sensations which occur are not alike in all cases, as Schröter<sup>1</sup> found in a number of patients, but are only now and then very distinct in many cases, and are not identical at every inhalation. In their typical form they consist, according to Pick,<sup>2</sup> in the appearance of an intensely yellow halo around any fixed point upon a clear background. This yellow circle is surrounded by a bluish-violet border. This phenomena is probably nothing more than the projection of the macula lutea, and the bluish-violet border its complementary color. The patients treated with nitrite of amyl by Sander<sup>3</sup> stated of their own accord, after the inhalation, that for some time everything had seemed yellow to them. It could not be clearly determined whether or not this phenomenon was due to the yellow color of that portion of the field of vision which corresponds to the

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<sup>1</sup> Schröter, *Zeitschrift f. Psychiatrie*, Bd. 32, 5, p. 527.

<sup>2</sup> Pick, *Centralblatt f. d. medic. Wissenschaften*, 1873, p. 866.

<sup>3</sup> Sander, *Medicin.-psycholog. Gesellsch. zu Berlin*. Sitzung vom 4. December, 1874.

macula lutea. The yellow vision disappears only after some minutes, growing gradually paler.

Schröter also noticed a diminution of the clearness of sight. Patients who had inhaled nitrite of amyl for a certain time were unable, *e. g.*, to see clearly the figures on a large clock, which seemed blurred to them. Normal vision returned immediately after they stopped using the drug.

An abnormal action upon the central nervous system is but seldom observed. Veyrières,<sup>1</sup> after a prolonged inhalation, noticed in his own case giddiness and stupor lasting from six to eight minutes, followed by a headache lasting two hours. In some cases of disease of the brain, Schröter witnessed, during the inhalation of the drug, the appearance, increase, or re-appearance of delirium of the senses. Bourneville<sup>2</sup> has reported similar observations. After the use of nitrite of amyl this author noticed violent headache, a feeling of dizziness, and in hysterical cases, visual illusions, accompanying the yellow sight produced by the agent.

After the inhalation of the drug, and to a certain extent as an after-effect, Sander observed profound collapse, which appeared suddenly and was characterized by fainting, falling to the floor, pallor of the face, smallness of the pulse, and cold clammy perspiration. Samelsohn<sup>3</sup> describes a similar case, in which a patient, while fully under the influence of nitrite of amyl, made a few deep, spasmodic inspirations, and presented coldness of the skin, which was bathed in sweat, and a small, thready, and extremely slow pulse, while consciousness, although weakened, was not entirely lost. Urbantschitsch<sup>4</sup> has also called attention to

<sup>1</sup> Veyrières, Virchow-Hirsch's Jahresbericht, 1875, i., p. 481.

<sup>2</sup> Bourneville, Gazette médicale de Paris, 1876, No. 13.

<sup>3</sup> Samelsohn, Berliner klin. Wochenschrift, 1875, p. 349.

<sup>4</sup> Urbantschitsch, Wiener medic. Presse, 1877, 8. u. ff.

the occurrence, in some cases, after the inhalation of even two drops of nitrite of amyl, of collapse, with paresis, or intense dizziness with difficulty of respiration.

With regard to other incidental effects, the statement of Bourneville is of interest, that tremor of the lips and difficulty of mastication often follow the inhalation of nitrite of amyl. Urbantschitsch noticed dryness of the mouth lasting from twelve to twenty-four hours after its use. In some cases, instead of redness of the face, the first effects of its action are palpitation of the heart, a sense of oppression in the head and ears, and tickling in the throat. The last symptom was observed by Veyrières also, while Ladendorf<sup>1</sup> noticed the occurrence of a violent dry spasmodic cough in a patient, on two occasions, during a four weeks' course of nitrite of amyl. A number of authors have also reported the occurrence of distressing nausea and vomiting after repeated inhalations of the agent.

In using nitrite of amyl, care must be taken that it does not present an acid reaction. After standing for a long time, decomposition takes place even in a previously neutral preparation, leading to the formation of free nitric acid. This change may be prevented by adding a few small pieces of burnt chloride of calcium, or a little magnesia to the preparation. The presence of hydrocyanic acid is readily demonstrated by shaking the nitrite of amyl with water, and testing the latter for this substance.

## EVACUANTS.

### I.—PURGATIVES.

#### OLEUM RICINI.

Some persons have an invincible repugnance to castor-oil, and often suffer from nausea and vomiting when they take

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<sup>1</sup> Ladendorf, Berliner klin. Wochenschrift, 1874, p. 539<sup>1</sup>



it. The latter also occurs if the oil is no longer fresh, and free fatty acids have formed in it. In order to disguise the unpleasant fatty taste of the oil and render it more palatable, numerous vehicles have been recommended, such as wine, brandy, milk, and coffee. Starke<sup>1</sup> advised for this purpose the conversion of the oil into a soft paste, by adding to it sugar (1 : 3) or compound liquorice powder (1 : 2) and to afterwards add to this, cinnamon powder or some other corrective.

#### ALOE.

Accompanying the special action of aloes (the production of pasty, not watery stools, with moderate griping), in addition to a sensation of warmth and oppression in the epigastrium, and frequent eructation, there not infrequently appear congestive conditions of other abdominal organs, such as the kidneys and uterus. Pre-existing hemorrhages, particularly from the latter organ, may be increased to a dangerous degree by the action of this drug. After large doses of aloes in substance or the extract, abortive effects are also said to have been observed. Under such circumstances the patients complain of pain in the region of the kidneys and uterus, and of a feeling of weight in the pelvis.

If preparations of aloes are used for a long time, there occurs, in consequence of the persistent congestion of the descending colon and rectum, dilatation of the hemorrhoidal veins, which may, in time, develop into true hemorrhoids. Whether this occurs to the extent described by Fallopius,<sup>2</sup> who says that, of one hundred persons who constantly use aloes as a purgative, ninety suffer from hemorrhoids, is, however, doubtful, in view of the numerous other unrecognizable conditions which contribute to the production of this affection. A certain predisposition

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<sup>1</sup> Starke, Berliner klin. Wochenschrift, 1879, p. 232.

<sup>2</sup> Fallopius: Opera omnia. De medicam. purg. simpl., Francoforti, 1600.

to the occurrence of the above-described effects is shown by aged and delicate young persons.

#### FRUCTUS COLOCYNTHIDIS.

Colocynth belongs to the class of drastic purgatives, which probably exercise their peculiar action by virtue of a direct irritation of the intestinal mucous membrane. For this reason, the stools are not infrequently attended with violent tearing pain and tenesmus, and may even be bloody, especially when the digestive tract is already in an irritated condition.

#### TUBERA JALAPÆ.

Like most of the other resins and substances which contain resins, which receive their cathartic properties by virtue of a direct action upon the intestinal canal, jalap root, which is active only in the presence of bile or bile-salts, usually excites pain and rumbling in the abdomen. Nausea sometimes occurs as the expression of gastric irritation. Vomiting may also take place. Large doses frequently repeated may excite catarrhal inflammation of the gastro-intestinal mucous membrane.

#### GAMBOGIA.

While small doses of gamboge, as a rule, produce no particular incidental effects, there appear, in some persons, even after 0.1–0.2 gram (gr. iss.–iij.), pain in the abdomen, vomiting, and a decided increase in the quantity of urine excreted.

#### HERBA GRATIOLÆ.

Gratiola, which was formerly much used as a cathartic, produces, as we learn from the numerous old publications concerning it, even in doses of 0.5–1 gram (gr. viiss.–xv.), in powder or decoction, not a cathartic effect, but nausea

and vomiting, or, besides these symptoms, salivation, burning in the urinary passages, loss of appetite, and attacks of nymphomania, as Bouvier<sup>1</sup> noticed, when the drug was used in women per enema. It is probable that the age of the drug and its richness in gratiolin, the active principle of gratiola, is influential in determining the occurrence of these symptoms.

#### FLORES SULPHURIS.

Sulphur, which has been much prescribed in a variety of chemical forms as a purgative, in the treatment of thoracic affections and chronic metallic poisoning, may easily produce irritation of the stomach and intestines, with digestive disturbances, particularly when the canal is already in an abnormal condition. It is partially transformed by the alkali of the intestinal juice into an alkaline sulphate, and, as this is decomposed by the carbonic acid of the blood and tissues, with the formation of absorbable sulphuretted hydrogen, the skin and the expired air both smell of this gas. According to Wibmer,<sup>2</sup> this agent in large doses may produce a miliary eruption.

When sulphur ointments are used, an artificial eczema is produced in some persons, which soon disappears after the use of the agent is stopped.

#### OLEUM TIGLII.

In addition to its drastic cathartic action, croton oil, taken internally, frequently produces, in certain persons, an itching, burning taste in the mouth, warmth and dryness of the throat, cructation, nausea, and colicky pains in different parts of the abdomen.

When applied to the skin as a derivative, there appears,

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<sup>1</sup> Bouvier, *Gazette de Santé*. Août, 1816.

<sup>2</sup> Wibmer: *Wirkungen der Arzneimittel*, v., p. 276.

after one or two applications, attended with itching and burning and slight fever, an erythema, and upon this there soon show themselves firm vesicles, with serous contents, sometimes discrete and sometimes running together. The contents become purulent one or two days after the vesicles burst, or there appear at once a large number of pustules, which form crusts within twenty-four hours. Secondly, there appear not infrequently, especially on the scrotum, as Wibmer<sup>1</sup> states, herpetic eruptions, which, perhaps, owe their origin to an accidental transplantation of the drug, but may also be regarded as a true absorptive affection. The former seems the more probable view, because such eruptions are never observed after the internal administration of croton oil. Tartar emetic, after the external application of which similar secondary eruptions are observed on the genital organs, produces eruptions when taken internally also, in which respect it differs from croton oil.

According to M. Langenbeck,<sup>2</sup> the endermatic employment of croton oil causes phlegmonous inflammation and suppuration.

The retrocession of the above-described skin affections takes place in from three to eight days after stopping the drug, and is attended with moderate desquamation. Only a pale yellow color of the affected portions of skin remains behind.

## II.—EMETICS.

### ANTIMONII ET POTASSII TARTRAS.

It is well known that tartar emetic, when applied to the skin, in solution or in the form of an ointment, produces

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<sup>1</sup> Wibmer, l. c., i., p. 215.

<sup>2</sup> M. Langenbeck: Die Impfung der Arzneikörper. Hannover, 1856, p. 84.

both eczema (papules, vesicles, œdema) around the mouths of the glands, as well as extensive pustular diseases of this organ (ecthyma antimoniale). The derivative method of treatment, in which this external application of antimony is still occasionally resorted to, causes intense pain to the patient. It is desired, as a rule, to produce only a slight inflammatory irritation, but instead of this, extensive tissue disturbances sometimes occur. Particularly during the application of the so-called "pox-salve" to the head, in the treatment of certain cerebral affections, such as dementia paralytica, there readily occur deep, crater-like, more or less complete losses of tissue, and sometimes even exfoliation of bone at the bottom of the lesion. Among the older reports upon this subject, mention should be made of that of Jacobi,<sup>1</sup> who, in the year 1819, saw in Würzburg several patients in whom, after the application of antimonial ointment to the entire scalp, both tables of the parietal bones were perforated, in consequence of a necrosis which resulted from the treatment. In view of such an occurrence, it is certainly not out of place to call attention to the fact, that Hebra long ago spoke in condemnation of such a "useless, injurious, and sometimes even dangerous proceeding."

The internal use of tartarized antimony as an emetic, either alone or in combination with ipecac root, as well as the use of other preparations of antimony, is sometimes followed, especially in children, by conditions resembling collapse, on account of the very great power of the drug to produce slowing and weakening of the action of the heart. For this reason it is advisable to administer analeptics, such as wine, coffee, etc., immediately after each attack of vomiting. To the same cause are to be attributed all those dangerous symptoms and even fatal results

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<sup>1</sup> Jacobi, Damerow's *Zeitschrift f. Psychiatrie*, Bd. xi., p. 369. Ref. in Schuchard, *Arzneimittellehre*. Braunschweig, 1858, p. 226.



which have been reported as occurring during the shorter or longer administration of antimony, even in small doses and in adult cases. It is probable that in such cases the individuality of the patient plays an important rôle. Thus, Falot<sup>1</sup> reports three cases in which, after from one to three small doses of antimony, there occurred, in addition to vomiting, delirium, and spasms, so great a prostration of strength, that life could be saved only by the energetic use of stimulants. Similar observations were made by Beau,<sup>2</sup> who reported two cases of death from small doses of antimony. In these also, the symptoms were from the first those of the most pronounced weakness of the heart, very small pulse, general cyanosis, and striking paleness of the face. Death took place, with increase of the prostration and coldness of the extremities. Although antimony is no longer employed so extensively as formerly, it is nevertheless still used as an emetic and expectorant often enough to justify this reference to the possibility of an injurious action.

Its employment in those who are the subjects of any pathological changes in the intestinal canal, no matter how insignificant they may be, such as catarrh, etc., should be carefully avoided, because, both after its external and internal use in such cases, inflammatory irritation and even deeper lesions of the gastric and intestinal mucous membranes are always produced. After its external application, this irritation occurs in consequence of an elimination of the metal into the stomach and intestines, as has been demonstrated by Radziejewski.<sup>3</sup> This inflammatory irritation is probably also the cause of the vomiting, which is the result of a reflex action set up by irritation of the central apparatus which presides over the

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<sup>1</sup> Falot, *Union médicale*, 1852, p. 245.

<sup>2</sup> Beau, *Bulletin de Thérapeutique*, September, 1856.

<sup>3</sup> Radziejewski, *Archiv f. Anatomie u. Physiologie*, 1871, p. 472.

movements of vomiting. Hyperemesis sometimes takes place.

The caustic action of tartar emetic, as well as other preparations of antimony, *c. g.*, Kermes mineral, also sometimes finds expression during the internal employment of medicinal doses, in the formation of pustules and vesicles in the mouth, throat, œsophagus, and even in the larynx. Laennec<sup>1</sup> regarded these symptoms as secondary, produced by a saturation of the body with the drug. Falck,<sup>2</sup> on the other hand, insisted upon the purely local origin of such affections from the action of the tartarized antimony introduced into the body in a fluid form, because they did not occur when it was taken in the form of pills. Although we cannot accept the theory of a saturation of the body with tartar emetic, we must admit the possibility of the occurrence of the changes above mentioned in consequence of the action of the antimony which circulates in the blood; because, after the administration of the agent, affections have been seen of the skin, and of mucous membranes which primarily never came in contact with it. Thus, it has been proven by numerous observations that not infrequently, after the external use of antimony, pustular eruptions develop secondarily, particularly on the genitals and inner surfaces of the thighs, even several weeks after inunction, without there having occurred a transportation of the drug by the fingers from the original point of application. Many cases have also been recorded in which, after the internal administration of tartarized antimony, pustular eruptions have appeared, by preference on the above-mentioned parts of the body, but also on others. Thus, Imbert-Gourbèyre<sup>3</sup> reports an observation of Gohlius,<sup>4</sup> in which, after a large dose of antimony, a

<sup>1</sup> Laennec, *Gazette des Hôpitaux*, 1853, No. 6

<sup>2</sup> Falck, *Canstatt's Jahresbericht über die gesammte Medicin*, 1853, v., p. 148.

<sup>3</sup> Imbert-Gourbèyre, *Gazette médicale de Paris*, 1861, pp. 3, 17, u. ff.

<sup>4</sup> Gohlius: *Medicin. practic., clinic. et forensis*. Lipsiæ, 1735.

red eruption appeared over the whole body. Boeck<sup>1</sup> also saw a similar phenomenon, after the administration of 0.6 gram (gr. ix.) of tartar emetic in the course of thirty-six hours. Helbert<sup>2</sup> reports a similar experience. Two possibilities present themselves, as Hermann states, for the explanation of this phenomenon. As its cause we must regard either an irritative action upon peripheral nerves, leading to reflex inflammatory changes in the blood-vessels, or a direct action upon the vessels themselves. In this manner engorgement of the capillaries of the skin, exudation, and later, the formation of pustules, would be brought about. It is, however, possible, that the glandular organs of the skin may be thrown into an inflammatory condition by the direct action of the drug.

The less severe forms of the antimonial eruption require no therapeutic interference. Extensive ulcerations should be treated according to ordinary surgical principles. The gastric symptoms require treatment, especially when a sense of weight and pain are felt in the epigastrium, and if only a short time have elapsed between the administration of the antimony and the appearance of these symptoms. For this purpose the stomach may be washed out, opiates or other narcotic substances being added to the fluid used. If hyperemesis be present, vegetable astringents, tannin, decoction of cinchona, etc., should be administered, because in such a case there is probably some antimony in the stomach, and it would form insoluble combinations with these agents.

#### RADIX IPECACUANHÆ.

Ipecac, which is now but seldom employed as an irritant to the skin, produces, as Bazin<sup>3</sup> found, when applied

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<sup>1</sup> Boeck, *Preussische Vereinszeitung*, 1843, No. 8.

<sup>2</sup> Helbert: *De exanthemat. arte factis*. Göttingen, 1844.

<sup>3</sup> Bazin: *Leçons sur les affections cutanées artificielles*. Paris, 1862, p. 106.

as an ointment (one part to two of lard), after two or three inunctions, a papular eruption, without disturbance of the underlying corium. Diffuse redness, with burning, first appears, and upon this small elevations are formed. These increase in size and number, and are attended with intense itching, while the skin between them may regain its normal aspect. They finally become quite large, and of an intense red color, showing no tendency to run together, and disappear under pressure. After stopping the inunction, the eruption takes a certain time, one or two weeks, to pass away. It finally disappears without desquamation or cicatrization. The itching persists until the eruption is entirely well. According to Delioux,<sup>1</sup> an ointment of ipecac, like tartar emetic, may produce umbilicated pustules, which, however, differ from those produced by the latter agent by healing without the formation of cicatrices.

The repeated internal administration of small doses of ipecac may, through the local action of the drug, excite gastric and intestinal catarrh, and as a consequence, loss of appetite and diarrhœa. The latter usually takes place in those cases in which the drug fails to excite vomiting. The stools are then less copious, being usually slimy, or bilious and slimy, and are often tinged with blood. According to Arnold,<sup>2</sup> ipecac not infrequently shows great differences in its action. Emesis is sometimes excited by 0.6 gram (gr. ix.), while in other cases 2.4 grams (gr. xxxvi.) produce no such effect. The cause of this difference lies partly in the individuality of the patient, and partly in the quality, origin, and age of the root.

Emetin, the alkaloid of ipecacuanha, is more constant in its action, but is also not free from the disadvantage of producing incidental effects.

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<sup>1</sup> Delioux, *Gazette de Paris*, 1852, No. 6 u. ff.

<sup>2</sup> Arnold: *Das Erbrechen und die Wirkung der Brechmittel*. Stuttgart, 1840.

## III.—DIURETICS.

## BULBUS SCILLÆ.

Squill and its active principle, scillitin, in addition to their diuretic action, sometimes produce nausea when given in small medicinal doses, and if such small quantities are taken for a long time, as in dropsical conditions, vomiting and watery diarrhœa with griping may occur. As its diuretic action becomes exhausted after a time, the drug is then usually ordered in larger doses. When this is done, the above-described symptoms may take place with greater intensity, and the patients may suffer from tickling and burning in the throat, attacks of colic, pain on micturition and even hæmaturia. These symptoms are the expression of a local irritant action of the agent upon the mucous membranes with which it comes into direct contact. The diminution in the frequency of the pulse, which is also often observed, is to be regarded as the result of an influence reflected from the stomach.

## RADIX SARSAPARILLÆ.

Gastric disturbances, such as nausea, inclination to vomit, and anorexia, and also general lassitude, are often observed after the use of large doses of sarsaparilla root. These symptoms are identical with those which have been noticed after the experimental therapeutic employment of smilacin, the active principle of the root.

## FOLIA TOXICODENDRI.

The officinal fresh leaves of the poison-sumach contain a yellowish-brown juice which is also found in the tincture of rhus toxicodendron. In recent times this agent is but rarely prescribed. It is, nevertheless, necessary to call attention to the fact that the fresh leaves and the tincture,



in doses not above the maximum limit, may produce, in certain persons, pains and gastro-enteric symptoms, also giddiness, deafness, delirium, and anæsthesia, and conditions simulating paralysis. In addition to these symptoms, there not infrequently appear, after the external application of the fresh leaves or the extract, violent itching, an erysipelatous redness and swelling of the skin, and also a vesicular or measles-like eruption, itching intensely, and disappearing only after some days, with desquamation. The emanations from the living plant are said to produce the same effect.

#### IV.—EXPECTORANTS.

##### AMMONII CHLORIDUM.

Sal ammoniac, introduced in small quantities into the stomach, produces no unpleasant effects. Nevertheless, the long-continued use of the drug in doses of one to two grams (gr. xv.—3 ss.) may give rise to derangements of digestion and loss of appetite. After taking four to eight grams (3 i.—3 ij.) and more, daily, Jacquot<sup>1</sup> observed diarrhœa and attacks of abdominal colic, and also nausea and vomiting.

##### ANTIMONII SULPHURETUM.

The sulphuret of antimony, which is sometimes used as an expectorant and resolvent, cannot be absorbed from the stomach, on account of its insolubility in water and dilute acids. It is, however, partially dissolved by the alkaline intestinal juices, as was proved by the experiments of L. Lewin,<sup>2</sup> and may then, as practical experience teaches, develop the complete action of antimony, as manifested by the production of vomiting and diarrhœa. The intensity with which this incidental action occurs depends upon the

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<sup>1</sup> Jacquot: Schuchardt's *Arzneimittellehre*. Braunschweig, 1858, p. 390.

<sup>2</sup> L. Lewin, *Virchow's Archiv*, Bd. 74.

quantity of the drug dissolved in the intestines, which varies with the degree of fulness of the stomach, for when this organ is well filled, the drug is carried, with that portion of the contents which escapes absorption, into the intestines, whence it may be discharged with the fæces. The incidental effects are therefore most intense when the stomach is nearly empty.

#### RADIX SENEGÆ.

Isolated statements occur in the older literature of the subject, concerning the incidental effects which appear after the use of senega. In some cases, after doses of 1 to 1.5 grams (gr. xv.–xxiv.) the drug is said to have caused a sensation of tickling and burning in the throat, increased flow of saliva, oppression over the stomach, nausea, vomiting and anorexia, symptoms which were followed by colicky pains and diarrhœa. Attention has recently been called to the fact that a drug is now and then sold as senega, even by respectable houses, which fails to produce the peculiar effects of this drug, and is not botanically identical with it.

#### V.—ANTIPARASITICS.

##### BALSAMUM PERUVIANUM.

Unlike other balsamic agents, balsam of Peru has been but rarely found to produce incidental effects. Mögling<sup>1</sup> has recently published an observation of the appearance of urticaria, lasting four days, after one inunction with this drug. After one evening rubbing upon his own person, on the arms, shoulders and breast, for the cure of scabies, about eight grams (3 ij.) of the balsam, he was affected with an uncomfortable feeling of heat of the body, and a burning sensation in the lungs, which was followed by a

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<sup>1</sup> Mögling, Berliner klin. Wochenschrift, 1880, p. 557.

spell of coughing. On the following morning, there appeared on the inner surface of the knee and on the shoulders, redness of the skin in patches, attended with intense itching. The latter symptom disappeared during the day, but returned at night. It originated in closely aggregated wheals, seated upon the thighs, sides of the abdomen, upper arms, and shoulders. At the same time he felt chilly and was nauseated, without his bodily temperature being elevated. Two days later, after inunctions with lard had been occasionally used with good results, for the relief of the local and general symptoms, and after the urticaria had successively attacked also the face, neck, back, forearms, forelegs, and the backs of the feet, he relieved himself from the trouble by means of a bath, and leaving off the woollen undershirt which he had worn during the four days of his illness.

According to Mögling, the congestion of the lungs may have been due to a taking-up of the drug by those organs, or, in view of the fact that he had long suffered from bronchitis and hæmoptysis, it might be regarded as the result of an injurious action upon a "*locus minoris resistentiæ*."

Less extensive eczematous eruptions upon the skin are occasionally observed as consequences of a local irritant action of balsam of Peru (perhaps only when a bad preparation is used), on places where it was applied for the cure of scabies. Such an occurrence may cause the observer to believe that scabies is still present, after the insects have long since been killed.

#### \* STYRAX LIQUIDUS.

Unna<sup>1</sup> observed albuminuria in patients suffering from scabies, who were being treated with styrax ointments. It occurred nine times in one hundred and twenty-four cases. A relatively large quantity of albumen suddenly

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<sup>1</sup> Unna, Virchow's Arch., Bd. 74.

appeared in the urine, and as rapidly disappeared. Unna believes that the tolerably large quantity of the balsam which is absorbed by the skin is the cause of this phenomenon. The passage of substances with a higher atomic weight through the walls of the renal capillaries, is said to make them permeable for albumen also, for a varying period.

#### RHIZOMA FILICIS.

##### *Extract. filicis maris æthereum.*

The root of male fern or its extract, which is much employed in large doses for the destruction of tape worms, has a disagreeable biting taste, and sometimes causes pains in the stomach and abdomen, nausea, vomiting, and diarrhœa. It is probable that the bad quality of the preparation employed is to blame for the production of these symptoms.

#### CORTEX RADICIS GRANATI.

After the administration of the bark of pomegranate root, in doses such as are usually given for the cure of tape-worm, particularly when the remedy is taken with too short intervals between the doses, there frequently appear nausea and vomiting, abdominal pains, and diarrhœa. Dizziness, a feeling of weakness, or temporary trembling of the limbs, are also not infrequently noticed after its use. According to Mérat,<sup>1</sup> the bark causes an increase in the secretion of urine. These symptoms disappear immediately after the use of the agent is suspended.

The variations in the mode of action of pomegranate bark are dependent upon the age of the preparation, since only the fresh root is capable of producing curative effects. In the use of a reliable preparation, small doses should be prescribed, and, since its action is exerted in a very short

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<sup>1</sup> Mérat, Gazette des hôpitaux, 1845, p. 115.

time, incidental phenomena are rare, and of only limited duration when they occur.

### SANTONINUM.

Wormseed, as well as its derivative santonin, almost always produces undesired effects by its administration in medicinal doses.

Neither santonin, which is insoluble in water, nor the soluble santonate of sodium, produces a red color when mixed with alkalies. This occurs, however, if they are first dissolved in alcohol, and then treated with alkalies. In the human body, santonin undergoes changes similar to those produced by alcohol in the drug. After it is taken in any form, and in small doses, 0.2 gram (gr. iij.) and more, in two or three hours the urine shows a yellow color, as if curcuma or chrysophanic acid had been added to it. White paper or linen dipped into it shows yellow spots when dried, a circumstance to which Martin<sup>1</sup> first called attention. If alkalies, such as soda-lye, ammonia, or an alkaline carbonate, are added to such urine, it becomes of a cherry-red color. The red color disappears spontaneously after from thirty to thirty-six hours, in contrast with the urine passed after taking rhubarb, the red color of which, produced by alkalies, is permanent, according to J. Munk.<sup>2</sup> According to this author, still further differences between these two kinds of urine are shown by the fact that the red color of the rhubarb-urine disappears under the influence of reducing agents (zinc-dust, sodium-amalgam), while that of santonin-urine resists their action, and also that baryta and lime-water added to rhubarb-urine throw down the chrysophanic acid with the deposit (the red color of which is not removed by wash-

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<sup>1</sup> Martin: Buchner's N. Repert. f. Pharmacie, Bd. ii., 1853, H. 5.

<sup>2</sup> J. Munk, Virchow's Archiv, 1878, p. 136.



ing), while in alkaline santonin-urine, under the same treatment, the pigment remains in solution.

Santonin-urine turns the plane of polarization to the left, as L. Lewin accidentally discovered. The changes which santonin undergoes in the body are unknown. Mialhe<sup>1</sup> believes that an oxidation-product, with the qualities of a weak acid, is produced. Its elimination by the urine can be demonstrated two or three days after it is taken, even in doses of only 0.2 to 0.4 gram (gr. iij.-vi.). If santonin-urine undergoes decomposition, the carbonate of ammonium which is produced, causes it to take on a red color, which may, under certain circumstances, such as the presence of vesical catarrh, lead to its being mistaken for bloody urine.

In some cases, strangury and itching in the urethra have been noticed after taking santonin.

Almost as constant as the changes in the urine are certain disturbances of the sense of sight, which show themselves after even small doses of santonin. They manifest themselves principally as yellow-seeing (chromatopsia), and sometimes last several hours. This phenomenon was first observed by Itzstein, and later by Spencer-Wells, but has been most carefully studied by Rose.<sup>2</sup> According to him, there occasionally appears before the real chromatopsia, after large doses of santonin, a violet color of the field of vision, which increases in intensity with the darkness of the objects looked at. All lighter bodies, windows, paper, etc., seem really yellow. Red and blue often appear in their complementary colors, orange and green, so that carmine-red objects seem pale, madder-red of a bronze color, and the sky and other blue objects green. This is, however, not always the case, and one also sometimes observes that, after taking santonin, red seems violent, or

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<sup>1</sup> Mialhe, *Comptes rendus*, xlvii., p. 413.

<sup>2</sup> Rose, *Virchow's Archiv*, Bd. xvi., p. 233 u. Bd. xviii., p. 15.

light and dark objects are taken by one person for orange, and by another for green.

This phenomenon is not due to a coloring of the ocular media by a product of decomposition of santonin, as was formerly believed to be the case, in analogy with the action of the coloring-matter of the bile in icterus, but is, according to Rose, the result of a nervous change in the retina. M. Schultze<sup>1</sup> adopts the view that the macula lutea experiences an increase in its yellow pigment through the action of santonin, and that, therefore, chromatopsia takes place. The entire absence of santonin in the ocular media, as well as the failure thus far to demonstrate it chemically in the retina, renders improbable a direct action of this substance upon the parts which receive the light, but does not, according to Herman,<sup>2</sup> exclude the possibility of its occurrence, on account of the fact that the changes are so slight, and, therefore, the quantity of the active substance is so small that it may entirely escape detection.

Among other changes in the eye, Martin observed an increased secretion of tears and a feeling of pressure, and others noticed spots before the eyes. While Rose denies the occurrence of amblyopia and accommodative disturbances, other authors, such Bianchi and Cogliesi<sup>3</sup> report amaurosis lasting two months and a half, in children, after medicinal doses.

Besides the eyes, the stomach is also affected by santonin, in many persons. Thus Martin experienced nausea after 0.4 gram (gr. vi.), and Rose observed vomiting after it. With these symptoms may be associated rumbling in the abdomen and eructation.

Rose has also reported the occurrence of nervous symp-

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<sup>1</sup> M. Schultze: Ueber d. gelben Fleck d. Retina. Bonn, 1866.

<sup>2</sup> Hermann: Lehrbuch der Toxikologie, Berlin, 1874, p. 384.

<sup>3</sup> Bianchi Cogliesi, Refer. in Husemann, Pflanzenstoffe, Berlin, 1871, p. 923.

toms of a central origin, such as olfactory and gustatory hallucinations, headache, and a kind of spiritual depression, collectively described as "santonin-intoxication."

Affections of the skin are very rarely produced by the use of santonin. Sieveking<sup>1</sup> has described a case of this kind. A child, who was given 0.18 gram (gr. iij.) of santonin for the cure of helminthiasis, vomited soon after taking it, and there then appeared an urticaria over the entire body, which, however, soon passed off. When 0.18 gram (gr. iij.) was again administered, general urticaria again showed itself, and the entire skin, particularly on the eyes, nose, and lips, became so much swollen and so œdematous that the face was totally unrecognizable. Salivation was also present. The sensorium was not affected. After a warm bath, all the symptoms disappeared in an hour.

#### BENZOLUM.

J. Munk<sup>2</sup> found, by experimenting upon himself, that benzole possesses a disagreeable, burning taste, and produces an almost caustic effect upon mucous membranes. Beginning with twenty-five, he took as much as fifty drops, in twenty-four hours, and afterwards experienced a feeling of fulness, weight, and burning in the epigastrium, and slight headache, while no marked effect was produced upon either pulse or respiration. According to Simpson,<sup>3</sup> the inhalation of benzole for the purpose of producing anæsthesia, is followed by unbearable roaring in the head, and Richardson noticed muscular spasms, difficulty of respiration, and convulsions, after using the drug in this manner.

A portion of the benzole is eliminated by the stomach in the form of a gas, as shown by the fact that eructations

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<sup>1</sup> Sieveking, *British Medical Journal*, Feb., 1871.

<sup>2</sup> J. Munk, *Pflüger's Archiv*, Bd. xii., p. 147.

<sup>3</sup> Simpson, *Monthly Journal Medical Science*, 1848, April.

occur soon after beginning the use of the agent, and last eight hours longer, having the odor and taste of coal-tar. Another portion enters into an organic group of atoms, and forms with it the "phenol-forming substance."

After the external application of this agent for the destruction of pediculi on the genital organs, care must be taken that it does not get in between the thighs and the scrotum. On this and other similarly sensitive parts, it produces intense pain, lasting several minutes, which is followed by a more or less extensive erythema.

#### ACIDUM PICRICUM.

Picric acid, which was formerly used as an astringent and tonic, and also as an anthelmintic, sometimes produces, after being used internally, as Seitz<sup>1</sup> has stated, an icteric discoloration of the skin and conjunctiva.

#### VI.—SUDORIFICS.

##### FOLIA JABORANDI.

After the use of jaborandi, made from the leaves of *Pilocarpus pinnatus* and *simplex*, the majority of observers report a series of objectionable incidental effects as attendants upon the normal action of the drug. The latter consists, as is well-known, in the occurrence of sweating, accompanied by a subjective feeling of warmth, in from ten to twenty minutes after taking, *e. g.*, four grams (fl. 3 i.) of an infusion of the leaves. It appears first on the skin of the abdomen and chest, later in the face, and finally on the upper and lower extremities, and lasts from about two to four hours. The secretion of a viscid saliva, which occurs simultaneously, or begins a little sooner, lasts the same length of time. According to Riegel,<sup>2</sup> the average

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<sup>1</sup> Seitz, *Deutsche Klinik*, 1855, 40.

<sup>2</sup> Riegel, *Berliner klin. Wochenschr.*, 1875, No. 46.

loss of weight after the sweating is 750 to 1,000 grams, (one to two pounds), but may amount to more than two kilograms (four pounds). A short time after taking the drug, the pulse becomes fuller, more frequent and softer, and later it often becomes smaller, with diminished force of the heart's action, facial pallor, and a subjective feeling of coldness.

Among the incidental effects which have been observed, mention should first be made of the vomiting which occurs from one-half to one hour after taking the drug, and which is always preceded by prolonged nausea. It is extremely annoying and exhausting to the patient, lasts for a long time, and may readily lead to dangerous collapse. In forty-one experiments, Riegel observed it eighteen times, and ten times nausea without vomiting. Lohrisch,<sup>1</sup> in thirty cases, saw violent vomiting twelve times, and nausea and inclination to vomit twenty-two times. The nausea showed itself sometimes immediately, sometimes half an hour, and even later, after taking the medicine. Bardenhewer<sup>2</sup> attributes the nausea and vomiting to the fact that, in consequence of its free secretion, small quantities of saliva are swallowed, and in this manner the very sensitive mucous membrane of the palate, the throat, etc., is irritated. Riegel accepts this explanation for only a part of the cases, as he witnessed the occurrence of vomiting also in patients who expectorated the saliva, instead of swallowing it.

After the nausea and vomiting, increased frequency of micturition is the most common symptom, occurring in about forty per cent of the cases. It appears so suddenly, and the desire is so great, that the patients are absolutely unable to resist it. Now and then a burning pain in the

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<sup>1</sup> Lohrisch, *Berliner klin. Wochenschrift*, 1875, No. 18, and *Inaug. Dissert.*, Berlin, 1875.

<sup>2</sup> Bardenhewer: *Ueber die therapeut. Wirkung des Jaborandi*, Bonn, 1875.



urethra and small of the back is also noticed, which is so intense as to draw loud cries of suffering from the patients.

The disturbances of vision so frequently noticed, to which Martindale first called attention, are also worthy of mention. The patients state that they are unable to see distinctly, because there seems to be a veil before their eyes. A few authors claim to have also observed dilatation of the pupils in these cases, but Riegel was not able to confirm this statement.

In addition to these incidental effects, there also occur not infrequently hiccough, dizziness, headache, with a kind of stupefaction, and, in some cases, a more or less intense chilliness, appearing near the close of the sweating stage, and also gastric and abdominal pains. After the cessation of the sweating, these symptoms also come to an end. In very weak persons, collapse without vomiting is occasionally observed.

#### PILOCARPINUM MURIATICUM.

After the discovery of the pharmacological qualities of jaborandi, numerous experiments were undertaken with a view to obtain its active principle in the hope that, by using it instead of the leaves, the obnoxious incidental effects might be avoided. Merk succeeded in obtaining the pure alkaloid, or its hydrochloric acid compound, in the form of a crystalline substance, with a slightly bitter and astringent taste, soluble in an equal quantity of water.

Although it has been found in the course of time that the use of this agent is also attended with a number of unpleasant symptoms, its quality of developing its activity from the subcutaneous connective tissue as a starting-point, causes it to present such great advantages over the leaves of jaborandi, that the latter must be placed much below pilocarpia as a diaphoretic. According to

the experiments of Weber,<sup>1</sup> one ccm. of a two-per-cent solution of the muriate of pilocarpia is equal to an infusion of five grams (gr. lxxv.) of jaborandi leaves in one hundred and twenty grams (fl.  $\frac{3}{4}$  iv.) of water. The quantity of saliva secreted after an injection of pilocarpia varies, according to Lösch,<sup>2</sup> with the individuality of the patient. The saliva itself is tough, viscid, and often as thick as the white of egg. The occurrence of salivation follows immediately upon the secretion of the sweat. In this respect also, the individuality of the patient plays a rôle, as is shown by the fact that some persons are bathed in sweat, while others transpire but slightly, after the same dose. Rigors are now and then observed during the sweating. Intimately associated with these phenomena is an increase in the frequency of the pulse, to the extent of thirty or forty beats in a minute. The patients often complain of palpitation of the heart, and very sensitive persons of a feeling of anxiety, which, however, speedily passes away.

Vomiting also occurs, and becomes very violent when it once begins. According to the statement of Lösch, this symptom occurs once in five times in women, but only once in ten times in men. It is usually followed by collapse. In children, in addition to vomiting, Demme<sup>3</sup> saw weakness approaching fainting, pallor of the face, and distressing hiccough. A burning sensation in the urethra or glans penis was also frequently noticed, usually associated with frequent micturition. Federschmidt<sup>4</sup> also observed dysuria in two instances. During the secretion of sweat and saliva, the patients sometimes complained of a feeling as if their bladders were full, and unable to empty themselves. When injections were again practised upon the same persons, these abnormal sensations failed to appear.

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<sup>1</sup> Weber, *Centrallblatt f. d. medicin. Wissenschaften*, 1876, No. 44.

<sup>2</sup> Lösch, *Deutsches Archiv f. klin. Medicin*, xxi., p. 258.

<sup>3</sup> Demme, *Centralzeitung für Kinderheilkunde*, 1877, No. 1.

<sup>4</sup> Federschmidt: *Zur Wirkung des Pilocarpin muriatic.*, Erlangen, 1877.

A disturbance of vision, characterized by mistiness, which frequently occurs, is also worthy of mention in this connection. In some persons with normal range and clearness of sight, this becomes so intense that, as Löscher states, they are unable to read large print six inches from the eyes. This phenomenon also presented itself in cases in which there was no increase in the lachrymal secretion.

The most unpleasant of all the incidental effects is, however, the collapse, which appears both during the stage of secretion, and after it, even in robust persons. The greatest attention must be paid to this symptom during the use of pilocarpia, because, if the possibility of its occurrence be ignored, a fatal result may easily take place. The heart must also be watched with the greatest care, particularly in persons with lesions of this organ, on account of the well-established enormous acceleration of its action, which is often attended with irregularity.

An observation of Ranke<sup>1</sup> may also be mentioned in this place. After the subcutaneous injection of 0.02 gram (gr.  $\frac{1}{3}$ ) of muriate of pilocarpia in a patient with uræmia, there appeared on the next morning, after the diaphoresis had passed off, a swelling of the submaxillary glands, to the size of a fist, and also of the parotids and tonsils, with fever. Under the use of atropia these phenomena passed off in the course of a day.

Great danger is incurred by the untimely use of pilocarpia in eclampsia. Sanger<sup>2</sup> reports three such cases, in which the injection of 0.02 gram (gr.  $\frac{1}{3}$ ) of pilocarpia was followed by œdema of the lungs. In one case, life was saved by the antidotal employment of 0.0006 gram (gr.  $\frac{1}{160}$ ) of atropia hypodermically, but death occurred in both the others. Sanger explains this injurious action of the drug by the deficient expectoration of the masses of mucus

<sup>1</sup> Ranke, Jahresber. f. d. ges. Medicin von Virchow-Hirsch, 1877, ii., p. 437.

<sup>2</sup> Sanger, Archiv f. Gynäkolog., Bd. xiv., H. 1.

which are formed under its influence, and their entrance into the lungs. Expectoration cannot be performed, because unconsciousness and loss of reflex activity are produced by the eclamptic attacks.

The fact that these abnormal phenomena were observed by a number of investigators, although they employed the same preparation, excludes the hypothesis that they were due to the quality of the drug. It seems probable that a certain disposition of the affected persons, and, perhaps, in some cases, also the improper doses of the agent employed, are responsible for their occurrence. As regards the latter factor, both Leyden<sup>1</sup> and Curschmann<sup>2</sup> state that the occurrence of collapse may be prevented by a very gradual increase of the dose. In view of previous experience, it must be confessed that it is beyond our power to prevent the occurrence of hurtful incidental effects, and we must, therefore, content ourselves with combating them as soon as they appear.

Atropia occupies the most important position as an appropriate remedy for this purpose, because it puts an end to both the sweating and the salivation, and also to the painful sensations, and arrests the vomiting. It should be administered either subcutaneously—five or ten drops of the following solution: Atropiæ sulphat., 0.1; Aquæ dest., 20.0 (gr. iss. : fl. 3 v.)—or internally, twenty to thirty drops every two hours of this solution: Atropiæ sulph., 0.01; Aquæ dest., 20.0 (gr.  $\frac{1}{6}$  : fl. 3 v.) until the symptoms are relieved. Collapse should be prevented by the administration of stimulants. Demme (l. c.) says that he avoids the majority of the hurtful incidental effects by giving brandy before making the injection. It is, as a rule, advisable to administer the pilocarpia before rather than after the principal meal, and, in view of the numerous

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<sup>1</sup> Leyden, Berliner klin. Wochenschrift, 1878, No. 27 u. 28.

<sup>2</sup> Curschmann, eod. loco, No. 25.

observations of collapse occurring in patients with cardiac valvular lesions, to regard diseases of the heart as contra-indications to the use of the drug. Ohms<sup>1</sup> also regards pilocarpia as contra-indicated in cases of gastric ulcer and in typhoid fever, because hemorrhages may be easily excited, in consequence of the great dilatation which the vessels experience under the influence of the drug.

### EMOLLIENTS.

#### GLYCERINUM.

The healing powers of glycerin upon wounds, which were particularly demonstrated by the experiments of Demarquay,<sup>2</sup> frequently fail to show themselves, or are even supplanted by directly opposite effects. This failure on the part of the agent is attributable to the impurity of the preparation employed. If it is placed in an impure condition upon wounds, upon eruptions on the skin, etc., there occurs a burning sensation at the point of application, lasting several hours, and a feeling of increased heat. At the same time, the affected part becomes swollen. Moist eruptions secrete more freely, and new pustules are formed under certain circumstances.

Absolutely pure glycerin applied to wounds produces only temporary burning, which is probably due to its hygroscopic powers. In using this agent, care must be taken that its specific gravity lies between 1.23 and 1.25, as prescribed by the Pharmac. Germanica. More highly concentrated preparations should not be used therapeutically, on account of their irritating properties.

#### OLEUM JECORIS ASELLI.

The peculiarly offensive odor and taste of cod-liver oil

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<sup>1</sup> Ohms, Petersburg medic. Wochenschrift, 1878, No. 6, p. 50.

<sup>2</sup> Demarquay : De la Glycérine, Paris, 1867.



produce at first, in different persons, usually adults, nausea, and even vomiting, during and after its administration, which are not repeated, however, if it is used for a long time. If too large doses are taken, diarrhœa occurs. Cod-liver oil sometimes produces eczema also, when used for several days. This observation of S. Bennett<sup>1</sup> is explained by the fact that, after large doses of the oil, the skin emits the peculiar odor of the volatile fatty acids in the oil. These, during their circulation in the body, reach the skin also, and there produce eruptions, probably by direct irritation. These are, according to Duclos,<sup>2</sup> always of a vesicular nature, and spread over the entire body.

### RUBEFACIENTS AND VESICANTS.

#### CHLORINUM.

Chlorine gas is irrespirable. Even when highly diluted with atmospheric air it is an energetic irritant to the mucous membrane of the air-passages, causing increased secretion of these parts, nasal catarrh, cough, oppression of the chest, and symptoms of genuine bronchitis.

If the gas acts upon the skin, there soon occurs an erythema, with itching, which disappears in a short time, with desquamation. Even in a diluted condition it produces pricking and itching of the skin; according to Schuchardt,<sup>3</sup> this organ is rendered more sensitive, and a papular eruption may appear, which ends in branny desquamation.

#### CANTHARIDES.

After the internal administration of cantharides or its tincture, in medicinal doses, a number of incidental effects

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<sup>1</sup> Bennett: *Treatise on the Oleum Jecoris Aselli*, London, 1841, pp. 16 and 47.

<sup>2</sup> Duclos, *Journal de Médecine*, Sept.-Novembre, 1846.

<sup>3</sup> Schuchardt: *Arzneimittellehre*. Braunschweig, 1858, p. 198.

manifest themselves, varying in intensity according to the individuality of the affected person. A burning sensation is experienced in the *primæ viæ*. After a time there occurs urgent desire to urinate, a burning feeling in the urethra, and frequent and painful erections. The last phenomena may develop into dangerous symptoms, after prolonged use of small doses, or after their increase without exceeding the ordinary limits. The mucous membranes of internal organs become the seat of more or less violent inflammation, and the consecutive symptoms of these changes show themselves, on the part of the stomach and intestines, in the form of nausea, vomiting, and diarrhœa, and on the part of the urinary passages as increased frequency of micturition, attended with the discharge of urine, sometimes containing blood, or albumen or morphological constituents, and on the part of the genital organs in the form of painful chordee.

The skin also sometimes manifests exanthematic disorders, in the form of erythematous or papular eruptions.

Of more importance than these effects of the internal administration of cantharides is a knowledge of those which appear after its external application. These changes, which correspond to those already described, may be produced by the application of a Spanish-fly blister, in consequence of the absorption of the active principle of cantharides. Thus Ledelius,<sup>1</sup> among others, noticed vomiting, strangury, and fever, after the application for three hours of a blister. These symptoms produced by absorption are the more intense, the more the portion of skin to which the agent is applied deviates from its normal condition.

The treatment of these symptoms consists in the immediate removal of the plaster, and cleansing the skin with soap. Mucilaginous beverages should be administered,

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<sup>1</sup> Ledelius, Refer. in Wibmer, *Wirkungen der Arzneimittel*, Bd. iii., p. 252.

to counteract the phenomena of irritation of internal organs.

#### FABA ANACARDII.

The Anacardium bean, popularly known as Cashew nut, contains within its pericarp a reddish-yellow substance, cardol, soluble in ether, alcohol, etc., which was recommended by Frerichs as a vesicant, under certain circumstances preferable to cantharides. The cardol prepared from *Anacardium occidentale* is known as cardoleum vesicans, that from *Semecarpus anacardium* as cardoleum pruriens. The latter is unfit for use on account of its property of producing dermatitis and even erysipelas. But after the application of *anacardium occidentale* also, the effect is often not a limited one, extensive inflammatory œdema and eczema being produced on remote parts of the body, *e. g.*, the face.

While this agent is but seldom employed by physicians, the anacardium bean is much used among the laity, and therefore frequently produces diseases of the skin. Thus E. Schwerin<sup>1</sup> found in the person of a woman who had placed one-half of a bean in her ear, to relieve toothache and pain in the face, an erysipelas of enormous extent. The face was bloated, both eyelids infiltrated, and the ear, the cheek, and the front of the neck, as low down as the clavicle, swollen and reddened. The external auditory canal, the external ear, and the adjacent portions of skin were covered with vesicles. Recovery took place in a few days.

In another case, in order to relieve pains in the chest, an anacardium bean was perforated longitudinally, placed upon a string and hung around the neck in such a manner that it lay over the manubrium sterni. Two days later, an

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<sup>1</sup> According to a previously unpublished observation which was kindly placed at my disposal.

erysipelas had developed, which covered the whole front of the chest, the mammæ, and the region of the shoulder as far up as the lower jaw, and presented a large number of vesicles upon its surface.

According to Bazin,<sup>1</sup> the oil expressed from the pericarp of the bean, when applied to the skin, also sometimes produces, within from six to twenty-four hours, one or more vesicles, the contents of which soon become purulent.

#### CORTEX MEZEREI.

Mezereon, which still occasionally finds employment as a vesicant, or for the application of superficial issues, produces vesicles upon the skin which may develop into ulcers. These are very painful, heal with extreme slowness, and are often accompanied by a pustular eruption around their edges.

After the appearance of the inflammatory phenomena, symptoms of systemic poisoning or even death may occur in consequence of the absorption of the drug. Such a case was studied by Pluskal.<sup>2</sup> Headache, dryness of the throat, cough, and fever appeared, and finally death took place, attended with loss of consciousness and convulsions.

#### SUMMITATES SABINÆ.

The use of the powdered tops of savine for the cauterization of condylomata, sometimes causes such intolerable pain that the use of the remedy must be abandoned.

After the internal administration of small and medium doses (0.3 to 0.8 grams) (gr. ivss.-xiiss.) as an emmenagogue, there occur digestive disturbances, and sometimes also vomiting and diarrhœa, strangury, and during menstruation, excessive loss of blood. In pregnant women, the too

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<sup>1</sup> Bazin, l. c., p. 119.

<sup>2</sup> Pluskal, Oesterreichische medic. Wochenschrift, 1842, No. 18, and 1844, No. 50.

prolonged use of small or of too large doses may induce abortion.

The action of *Oleum Sabinæ* is more intense than that of the tops.

#### CHRYSAROBINUM.

##### *Goa-Powder.*

A secret remedy, "Araroba-powder, or Goa-powder," has long been employed in the treatment of skin diseases in England, Brazil, and the East Indies. The tree which furnishes the powder is most common in the province of Bahia. The araroba, in the form of a sulphur-yellow powder, is found in the crevices and cavities which traverse the tree in the direction of its transverse diameter.<sup>1</sup> According to a previous analysis, the powder should contain eighty-four per cent of chrysophanic acid. Liebermann<sup>2</sup> showed, however, that the substance obtained from goa-powder by extracting it with benzole, was not chrysophanic acid, but a body of different chemical composition, which he called chrysarobin. It may be transformed into chrysophanic acid by the addition of potash-lye and the admission of air.

Balmanno Squire<sup>3</sup> first employed this agent in the form of an ointment, in the treatment of psoriasis, and afterwards of eczema, acne, etc., with good results. Numerous therapeutical experiments were afterwards made in Germany with chrysarobin. The ointment is usually applied upon the skin after the psoriatic scales are removed, either mechanically or by chemical means (green-soap, etc.).

All the experimenters who used chrysarobin report unpleasant incidental effects after its application, which appeared as local and general symptoms. These have

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<sup>1</sup> Vierteljahrschrift f. Dermatolog. u. Syphilis, vi., 1879, p. 385.

<sup>2</sup> Liebermann, Berichte der deutsch. chem. Gesellschaft, Jahrg. xi., p. 1603.

<sup>3</sup> Balmanno Squire, British Medical Journal, May and November, 1877.



been best described by Kaposi.<sup>1</sup> If chrysarobin is rubbed upon psoriatic patches, there appears, early in some persons, later in others, an inflammation at the point of application, which may spread over a large extent of the healthy skin. Many individuals seem especially predisposed to this accident, and in such cases the inflammation increases inordinately in intensity and extent. The face and the genitals seem to possess a peculiar sensitiveness to chrysarobin ointment.

Three forms of inflammation occur, according to Kaposi:

1. A diffuse inflammatory redness and swelling. In many cases this appears as a halo of varying breadth around each patch of psoriasis, after from four to six in some, in others after from eight to fifteen applications. If no more inunctions are made, this redness disappears after from ten to fourteen days, with desquamation of the epidermis. But in spite of the cessation of the applications, the inflammation and swelling often spread still further, and cause pain, fever, sleeplessness, glandular swelling, etc., in short, the general symptoms which are usually observed after a diffuse dermatitis.

2. The inflammation may also manifest itself by the appearance of pin-head sized, reddish-brown, firm papules, some of which also present vesicles and pustules. They correspond to the openings of the follicles. The patient complains of annoying itching and burning.

3. Painful furuncles may also be developed.

For the relief of the pain and the inflammation, the application of cold-water compresses has been recommended. In order to prevent these irritations of the skin, Neumann advised the protection of the parts around the diseased patches by strips of adhesive plaster. Others believe that the unpleasant effects of the drug may be avoided by

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<sup>1</sup> Kaposi, Wiener medicin. Wochenschrift, 1878, No 44.

gradually increasing the proportion of chrysarobin in the ointment. Kaposi advises against the use of the agent on the face, and directs that it be employed on the genitals only after careful isolation of the adjoining folds of skin, and that the application be suspended, as soon as inflammatory areolæ have formed around the patches of psoriasis.

A discoloration of the tissues which come into contact with the drug nearly always occurs as an accessory symptom of the above-mentioned incidental effects. The normal skin, as well as the nails, take on a reddish or violet-brown appearance, and the hair becomes of a golden-yellow or of a variegated greenish color. If soap is used upon parts thus deprived of their normal color, the reddish-brown color is changed into dark violet, in consequence of the action of the potash upon the chrysarobin. This transformation of color is most marked on the inflammatory ring which forms around the psoriatic patches. The underclothing of the patients, like the skin, becomes covered with spots of a more or less purple-brown or violet color, which are very hard to remove.

#### ACIDUM PYROGALLICUM.

Pyrogallic acid was introduced into the treatment of skin diseases by Jarisch.<sup>1</sup> Only insignificant incidental effects show themselves after its employment. Applied to psoriatic patches or the normal skin, it produces a brown discoloration. On the extremities it excites localized inflammation, which may lead to epidermic desquamation and the formation of vesicles. When applied to hard, infiltrated patches, the ointment produces deep losses of tissue, reaching down to the corium. The scars left behind, after cauterizing lupus nodules with pyrogallic acid, are smooth, white, and flexible. Jarisch, after the use of the

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<sup>1</sup> Jarisch, Wiener medic. Jahrbücher, 1878, H. iv.

acid in eczema marginatum, observed pain lasting several days, and increasing when the dressings were changed.

Instigated by the success obtained by Jarisch, Neisser<sup>1</sup> also tried pyrogallic acid in the case of a man afflicted with psoriasis universalis. For purposes of comparison the right arm and leg, and the back, were energetically rubbed with unguentum Rhei (Extr. Rhei spirit. in the form of a twenty-per-cent ointment), the left side and the breast with pyrogallic acid, and finally smeared with a thin layer of the ointment, and then the whole body was covered with rubber paper, which was secured by roller bandages. A few hours after this operation there appeared rigors, diarrhoea, and vomiting, which lasted three days, until death occurred in collapse. The urine contained the coloring matter of the blood. The autopsy revealed as the causes of death, decomposition of the blood, nephritis hæmoglobinica, and a disseminated fatty degeneration of the muscular tissue of the heart.

The majority of the symptoms observed in this case were undoubtedly due to the arrest of the bodily perspiration, because the effect of so extensive an application must be the same as that of varnishing the whole body.

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<sup>1</sup> Neisser, Zeitschr. f. klin. Medicin, Bd. i., Heft 1.



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